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Well begun is half done:

Preoperative Physical Performance and Home-based Exercise in
Older Adults undergoing Abdominal Cancer Surgery

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Well begun is half done: Preoperative Physical Performance and Home-based Exercise in Older Adults undergoing Abdominal Cancer Surgery

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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From a global perspective...

“Years have been added to life, now we must add life to years”

— WHO

To the individual...

“... I got tired back in February without knowing why, which resulted in reduced ability to do things I normally do. You might blame age, but it was not age, it was the disease.”

— Participant in the interview study

ABSTRACT

The proportion of older adults continues to increase in Sweden and globally. Consequently, we are seeing an increase in diseases associated with aging, such as cancer. The primary treatment for abdominal cancer is surgery, and older adults receive surgery to a greater extent today. However, they have more requirements and other outcomes than younger people due to different physiology, limited reserve capacity, heterogeneity and a greater presence of comorbidities with increasing chronological age. Physical performance is a modifiable preoperative factor. If optimized, it might have the potential to reduce adverse postoperative events, which is important for both the individual and economically for society. The overall aim of this thesis was to determine how preoperative physical performance was associated with postoperative outcomes, and to increase knowledge regarding supervised home-based physical exercise as a potential intervention prior to abdominal cancer surgery in older adults.

This thesis consists of four papers based on three clinical studies, including people ≥ 70 years of age undergoing abdominal cancer surgery. In **study A (papers I and II)**, a prospective cohort study (n=197, and subgroup n=140), we showed that better preoperative physical performance was associated with reduced adverse postoperative outcomes. On both the micro (complication severity and in-hospital mobility), and meso levels (discharge destination, and length of stay). These results indicate that screening of physical performance (in combination with conventional preoperative risk assessments) can provide additional information for decision-making regarding each patient's surgical pathway, and hopefully facilitate shared decision-making with the patient. In **study B (paper III)**, a feasibility study with a randomized control design (n=23), we reported that a short-term, supervised, home-based exercise program at a high level of exertion was feasible with respect to compliance and acceptability, in older adults prior to colorectal cancer surgery. However, recruitment was low and needs to be improved to reduce the risk of recruitment bias. When further investigating preoperative exercise, in a qualitative interview study (**study C, manuscript IV**, n=17), the patients described a gap between awareness of the benefits of being physically active and actually being physically active prior to surgery. The patients perceived multiple influencing factors and expressed a need for active support and guidance from health care to enable action, which should be considered during the preoperative period.

The findings of this thesis emphasize the importance of physical performance rather than chronological age. It addresses the additive value of a functional approach regarding both objectively measured physical performance and physical exercise in preoperative care, to place the older individual in focus. Perceptions from older adults scheduled for abdominal cancer surgery underlines the importance of preoperative guidance and support to enable physical activity and exercise. In addition, the thesis adds information regarding the magnitude of short-term physical decline and factors associated with postoperative mobility, which is important to understand in regard to postoperative recovery.

SVENSK SAMMANFATTNING

Andelen äldre ökar i Sverige och globalt, vilket leder till en ökning av sjukdomar förknippade med åldrande såsom cancer. Den primära behandlingen för cancer i mag-tarmkanalen är kirurgi, och äldre genomgår kirurgi i allt högre utsträckning. De har emellertid andra behov och utfall än yngre personer på grund av olika fysiologi, begränsad reservkapacitet, heterogenitet och en högre förekomst av samsjuklighet. Fysisk förmåga är en faktor som vi kan påverka innan en operation, och en optimering kan potentiellt minska negativa hälsoutfall postoperativt, vilket är viktigt för både individen och ekonomiskt för sjukvården och samhället. Det övergripande syftet med denna avhandling var därför att undersöka associationen mellan preoperativ fysisk förmåga och postoperativa utfall, samt att öka kunskapen om övervakad, hembaserad fysisk träning som en potentiell intervention för äldre innan bukkirurgi pga. cancer.

Denna avhandling består av fyra vetenskapliga artiklar baserade på tre kliniska studier som involverar personer över 70 års ålder som genomgår bukkirurgi pga. cancer. **Studie A (artikel I och II)**, en prospektiv kohortstudie (n=197, respektive n=140), visade att bättre fysisk förmåga innan bukkirurgi minskade oddsen att drabbas av negativa hälsoutfall såsom högre komplikationsgrad, begränsad förflyttningsförmåga, och utskrivning till vidare vård, efter operationen. Resultaten indikerar att kartläggning av fysisk förmåga, i kombination med sedvanlig preoperativ bedömning, kan ge ytterligare information för beslutsfattande angående varje patients preoperativa väg och förhoppningsvis bidra till ett delat beslutsfattande med patienten. I **studie B (artikel III)**, en genomförbarhetsstudie av en randomiserad interventionsstudie (n = 23), rapporterade vi att ett övervakat träningsprogram i deltagarens hem på en hög ansträngningsnivå var genomförbart med avseende på följsamhet och accepterbarhet hos äldre som ska genomgå bukkirurgi pga. tjock- och ändtarmscancer. Rekryteringen var emellertid låg och behöver förbättras för att minska risken för rekryteringsbias. Vid vidare undersökning av ämnet preoperativ träning i patientgruppen, genom en kvalitativ intervjustudie (**studie C, manuskript IV**, n = 17), uppfattade deltagarna ett glapp mellan en medvetenhet om fördelarna med att vara fysiskt aktiv och att faktiskt vara fysiskt aktiv innan en operation. Deltagarna beskrev flertalet faktorer som påverkade detta glapp i positiv eller negativ riktning, och uttryckte ett behov av aktivt stöd och vägledning från sjukvården för att möjliggöra preoperativ aktivitet och träning.

Resultaten av denna avhandling betonar vikten av fysisk förmåga snarare än kronologisk ålder innan bukkirurgi pga. cancer. Den belyser ett funktionellt perspektiv avseende både mätningar av fysisk förmåga och preoperativ fysisk träning och sätter den äldre individen i fokus. Uppfattningar från äldre som planeras för bukkirurgi pga. cancer betonar vikten av preoperativ vägledning och stöd för att möjliggöra fysisk aktivitet och träning. Avhandlingen adderar också information om storleken på postoperativ funktionsförsämring och faktorer som är associerade med postoperativ funktionsförmåga, vilket är viktigt att förstå i relation till postoperativ återhämtning.

LIST OF SCIENTIFIC PAPERS

The following four papers, referred to by their roman numerals in the text, form this thesis:

- I. Karlsson E, Egenvall M, Farahnak P, Bergenmar M, Nygren-Bonnier M, Franzén E, Rydwik E.
Better preoperative physical performance reduces the odds of complication severity and discharge to care facility after abdominal cancer resection in people over the age of 70—A prospective cohort study. *Eur J Surg Oncol.* 2018;44:1760-1767. doi: 10.1016/j.ejso.2018.08.011.
- II. Karlsson E, Franzén E, Nygren-Bonnier M, Bergenmar M, Rydwik E.
Short-term postoperative physical decline and patient-reported recovery in people aged 70 or older undergoing abdominal cancer resection. *J Geriatr Oncol.* 2019;10:610-617. doi: 10.1016/j.jgo.2019.01.004.
- III. Karlsson E, Farahnak P, Franzén E, Nygren-Bonnier M, Dronkers J, van Meeteren N, Rydwik E.
Feasibility of preoperative supervised home-based exercise in older adults undergoing colorectal cancer surgery: A randomized controlled design. *PLoS ONE.* 2019;14(7):e0219158. doi: 10.1371/journal.pone.0219158.
- IV. Karlsson E, Dahl O, Rydwik E, Nygren-Bonnier M, Bergenmar M.
Mind the gap between awareness and action: Older patients' attitudes towards, and perceptions of, preoperative physical activity and exercise prior to colorectal cancer surgery—a qualitative study. *Submitted manuscript.*

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Some additional calculations are added in the results section of this thesis.

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
ANOVA	Analysis of Variance
AUC	Area Under the Curve
CAM	Confusion Assessment Method
CCI	Comprehensive Complication Index
CGA	Comprehensive Geriatric Assessment
CI	Confidence interval
CPET	Cardiopulmonary exercise test
CRC	Colorectal cancer
CST	Chair Stand Test
HRQoL	Health-related quality of life
IMT	Inspiratory Muscle Training
IQR	Interquartile range
LoS	Length of Stay (in hospital)
MCT	the Movement Continuum Theory
MIP	Maximal Inspiratory Pressure
MMSE	Mini-Mental State Examination
MNA-SF	Mini Nutritional Assessment Short Form
OR	Odds Ratio
PASE	Physical Activity Scale of the Elderly
PPC	Postoperative Pulmonary Complications
PROM	Patient-reported outcome measure
PRP	Postoperative Recovery Profile
PSFS	Patient Specific Functional Scale
RCT	Randomized Controlled Trial
ROC	Receiver Operating Curve
RRR	Relative Risk Ratio
sd	Standard deviation
SVF	Standardized Care Procedures
WHO	World Health Organization
6 MWT	Six-minute walk test

PREFACE

Since my graduation from the bachelor program in physiotherapy at Karolinska Institutet in 2009, my interest in hospital-based in-patient care, and especially in the older population, which constitutes the majority in Swedish health care, has increased exponentially. This is due to the everyday interaction with the patients and with colleagues of different disciplines, the symbiosis of different fields, and the endless learning opportunities. My interest in improving care for the older population in daily clinical settings (through sustainable assessments and long-term interventions), and in increasing collaboration between in- and outpatient care has been central in my project and throughout my training. The project has enabled me to broaden my preventive perspective, and to reason how we can be able to prepare the people who might need it the most without losing focus on the patient.

Stepping into these four intense years, my belief was that the courses and literature would guide my knowledge development. Many things have changed since then. First, I have come to realize that the people who have crossed my path during this journey are the ones from whom I have learned the most. So my greatest appreciation goes to the participants in the studies, the various professionals involved at the hospital and primary care sites, and in the progression of the scientific process of the papers, as well as the researchers who guided me.

Second, the phrases “learning by doing” and “facing reality” have never been more accurate as the challenges of how to conduct research turned into the meaningful factors. The research plan has changed multiple times over these years, facilitated by the results of each study, which have finally linked them together into a meaningful overall thesis. Nevertheless, my personal belief in conducting research to enable everyday clinical decisions based on scientific evidence to provide the best care for older patients has stayed rock-solid. This thesis has created the corner pieces of the puzzle, hence the majority of the pieces are yet to be put in place, by myself and/or others.



Emelie Karlsson

Stockholm, 23rd of October 2019

1 INTRODUCTION

Older adults undergo surgery and survive cancer to a greater extent today, meaning that more people live longer with or beyond cancer and its multidimensional consequences (1-3). One-fifth of the Swedish population is ≥ 65 years of age, and the proportion is estimated to be one-fourth by the year 2070 (4). This generates an increase in diseases associated with aging, such as cancer. Many cancer types, for example colorectal cancer, can be considered a disease of older adults nowadays and the incidence is predicted to keep rising (3, 5). In 2016 there were 17.2 million cancer cases worldwide (6) and 65,000 malignant tumors in Sweden (3). Given the higher proportion of older adults, it has been predicted that by the year of 2035, 60% of cancer cases will be found in adults aged 65 or above, compared to 47.5% in 2012 (7).

This creates a higher burden of disease and possible disability for both the individual and economically for society. Older adults scheduled for surgery have other requirements and outcomes than younger people due to different physiology, limited reserve capacity, heterogeneity and a greater presence of comorbidities with increasing chronological age. Physical performance and reserve capacity are modifiable preoperative factors in which physical therapy assessments and interventions play a crucial role for optimization. The preoperative process, including preoperative optimization, is an emerging area both in research and in the clinic, and the individual's needs may differ substantially during the care trajectory (8). Therefore, in perioperative care we need to consider assessments and outcomes on both the micro and meso levels (9, 10). Micro level means the patient level and meso level the health care organization level, which in this thesis includes hospital and primary care (figure 1). Both of these are required in the long run to affect the macro (policy) level and enable future implementation of new research into practice.

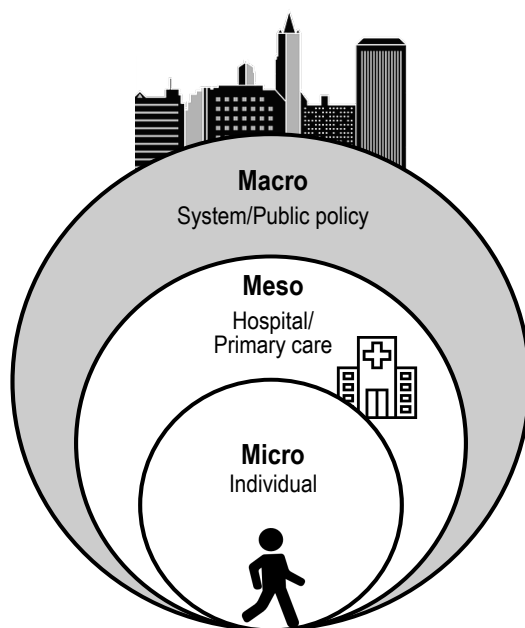


Figure 1. Illustration of micro-, and meso levels in relation to this thesis (the macro level is seen in future directions). Icons made by [freepik and mynamepong] from www.flaticon.com

2 BACKGROUND

2.1 GERIATRIC ONCOLOGY

Variability in health status increases with chronological age, whereas assessments and individually tailored interventions in geriatric oncology are of great importance. Added to the aging process, comorbidities, defined as “the combination of additional diseases beyond an index disorder,” are more frequently present (11). Thus, in the onco-geriatric context there is not only a considerable heterogeneity among individuals regarding general health, and cancer diagnosis, but also an influence from comorbidities and physical impairments (7, 8).

Therefore, it is important to move away from a focus solely on disease and start combining it with modifiable biological factors and daily functioning.

In addition, within geriatric oncology, frailty (a state of increased vulnerability based on reduced physiological function) appears more frequently, with a median incidence of 42%, than in healthy older adults (12). It has previously been suggested as a better predictor of postoperative mortality and complications compared to chronological age in various surgical populations (13). However, there is a large individual variation in the older population, as suggested by the Clinical Frailty Scale, which presents conditions from very fit, well, managing well, vulnerable, to different states of frail (14, 15). Individuals in several of these stages might need physical optimization, not just the frail ones.

The complexity of older adults' health has resulted in suggestions for structured approaches for action. Early on, progress and challenges in geriatric oncology were addressed in research (16), merging an oncological and geriatric approach incorporating assessments of e.g. comorbidity and activities of daily living (ADL) in cancer care. The comprehensive geriatric assessment (CGA), a multidomain assessment of an older patient, was suggested as a way of assessing and tailoring the surgical pathway for the older population in oncology (17, 18). However, sometimes the CGAs lack an objective assessment of physical performance, which is an important supplement to enable a focus on function and patient needs.

2.2 ABDOMINAL SURGERY

More than 112 000 surgical procedures on the gastrointestinal tract and associated organs were conducted in Sweden in 2017. Almost half of these involved people over the age of 65 years (19). Abdominal surgery is considered to be a high-risk surgery due to high rates of postoperative complications (20). Colorectal cancers, taken together, are the third most common cancer forms in Sweden and globally (21, 22). The primary treatment for abdominal tumors is surgery. Synchronous liver metastases are present in primary colon or rectal tumors in 15% of cases initially, and an additional 15% within 5 years of diagnosis (22). The incidence of neoadjuvant chemotherapy is 5% before colon cancer surgery in people < 75 years and is even more rare in older ages, whereas radiotherapy is more common prior to rectal cancer surgery (23). The incidence of pancreatic tumors is lower, but given the high

mortality rate and extensive surgery, pancreatic cancer gives a greater burden of disease for the individual. Only 20–25% of pancreatic tumors are treated with surgery (24); thus a pre-selection of the fittest individuals might occur in the pancreatic surgical population.

From 2015 to 2018, the Swedish Government and the Swedish Association of Local Authorities and Regions agreed on a national investment to shorten the waiting period and reduce regional differences in cancer care. The aim of the standardized care procedure (SVF) is that “cancer patients should experience a well organized, professional and holistic cancer care without unnecessary waiting time in connection with the preoperative investigation and treatment” (25). The time aspect is based on the shortest time that can be achieved when taking the medical conditions and health care organization into consideration.

2.3 PHYSIOLOGICAL CHANGES DUE TO SURGICAL STRESS AND AGING

Surgical stress induces catabolic changes and increases the demands on all organ functions (26-28). The types of anesthesia, the surgical incision site and surgical approach have further influence. Regarding the cardiovascular, respiratory and musculoskeletal systems, water retention and increased cardiac output increase the load on the heart (28). Increased oxygen consumption and reduced lung volumes are the primary causes of atelectasis and pulmonary complications (mainly in upper abdominal surgery). Dysfunction of our primary respiratory muscle, the diaphragm, also increases this risk (26). In addition, immobilization and an impaired ability to take deep breaths may occur due to pain. Hypermetabolism (such as proteolysis and lipolysis) leads to insulin resistance and increases the risk for protein loss. Protein catabolism, triggered by surgical stress, mainly effects skeletal muscle protein and can lead to considerable loss of lean body mass after major abdominal surgery (27).

If we add an average of 1% functional decline of the organ systems a year from the age of 40 (29), one would hypothesize an increased risk of postoperative adverse outcomes such as complications, increased care needs and functional decline in some older adults. The aging process creates different challenges in preoperative care than in younger individuals. A natural decrease in cardiovascular capacity, respiratory function, and muscle mass occur in the aging process due to gradual damage on the molecular and cellular levels (2, 30). Blood vessels stiffen, increasing the risk of systolic hypertension and creating a greater load on the left ventricle of the heart, leading to an increased risk for atrial fibrillation (2). There is also a reduction in compliance of the chest wall, the strength of the respiratory muscles and changes in the lung parenchyma. Body composition changes and muscle mass decreases, which affects muscle strength and function (1, 2, 31). All this limits resilience to cope with the demands of a temporary stressor such as surgery (30, 32). Therefore, it is important to maintain homeostasis when multiple risk factors become manifest at the same time.

2.4 PREOPERATIVE PHYSICAL THERAPY

Current physical therapy intervention in clinical practice prior to abdominal surgery in Sweden (2019) is preoperative information, with regional differences. It often consists of brief verbal or written education regarding the effects of surgery on the respiratory system, techniques for getting in and out of bed, postoperative respiratory exercise, and general recommendations of 150 minutes of moderate physical activity a week. This approach might not be appropriate or enough for vulnerable older patients facing major surgery. As previously mentioned, due to the heterogeneity in the older population not all are in need of optimization, and there is a need to identify older adults at risk of postoperative adverse outcomes. This is schematically described in a hypothetical model in figure 2.

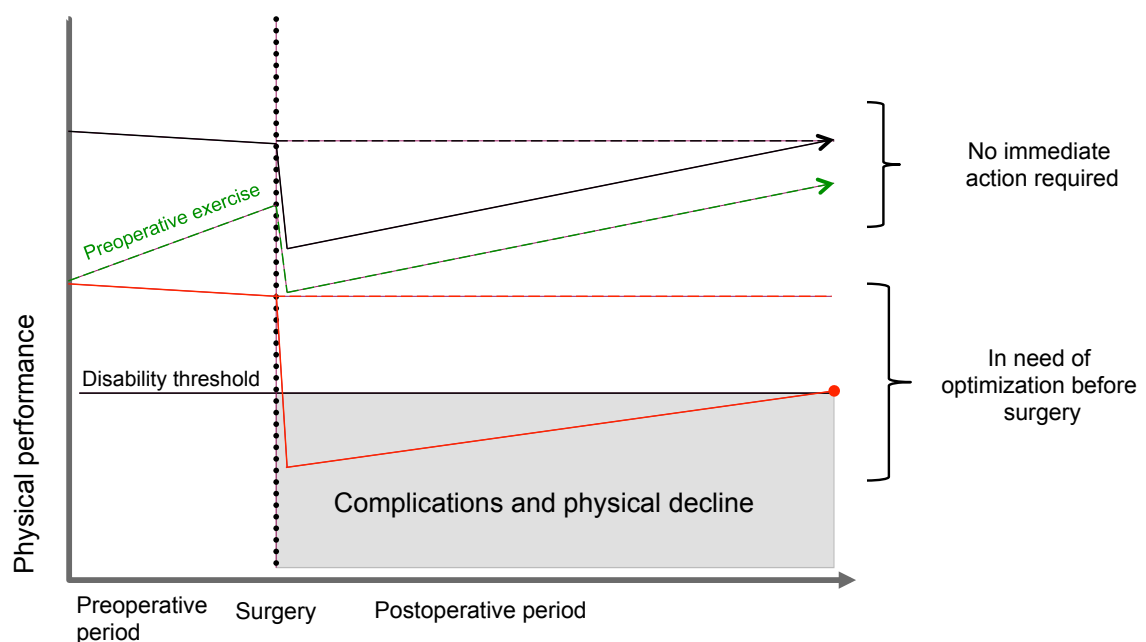


Figure 2. Hypothetical model demonstrating the possible effect of preoperative physical performance on postoperative outcomes and recovery, modified from Topp et al (33) with print permission from AACN (American Association of Critical-Care Nurses) Advanced Critical Care.

2.5 THEORETICAL FRAMEWORK

The conceptual approach of this thesis is based on the Movement Continuum Theory (MCT) (34), with the aim of putting physical therapy into a theoretical context. Cott et al. described the construct of movement, defined as a change in position, and the theory as a “potential base for movement assessments and interventions.” Further developments by Allen proposed a six-dimension model called the Movement Ability Measure, making the MCT more clinically applicable (35, 36). The six dimensions of the Movement Ability Measure are flexibility, strength, speed, accuracy, adaptability, and endurance. The first three dimensions are involved in all human movement, and accuracy takes into account the aspect of movement being purposeful. Lastly, the ability to adapt to and endure a current change, disease, or stressor is crucial, and highly relevant in the preoperative context, both dealing with a cancer diagnosis and preparing for surgery.

Reviewing movement and physical therapy through this theory emphasizes the variation in movement abilities between and within individuals, which facilitates the possibilities of identifying and tailoring assessments and interventions to each individual’s needs. The MCT describes that an individual has three stages of movement capability, “a maximum, a current, and a preferred” (figure 3) (34, 37). If we identify movement capabilities by assessments, and then intervene where needed, the discrepancy between the current and preferred capability can be decreased (37). A weakness of the theory in the context of this thesis is that it does not fully consider an individual’s perspective, such as expectation, motivation, and ability to adapt.

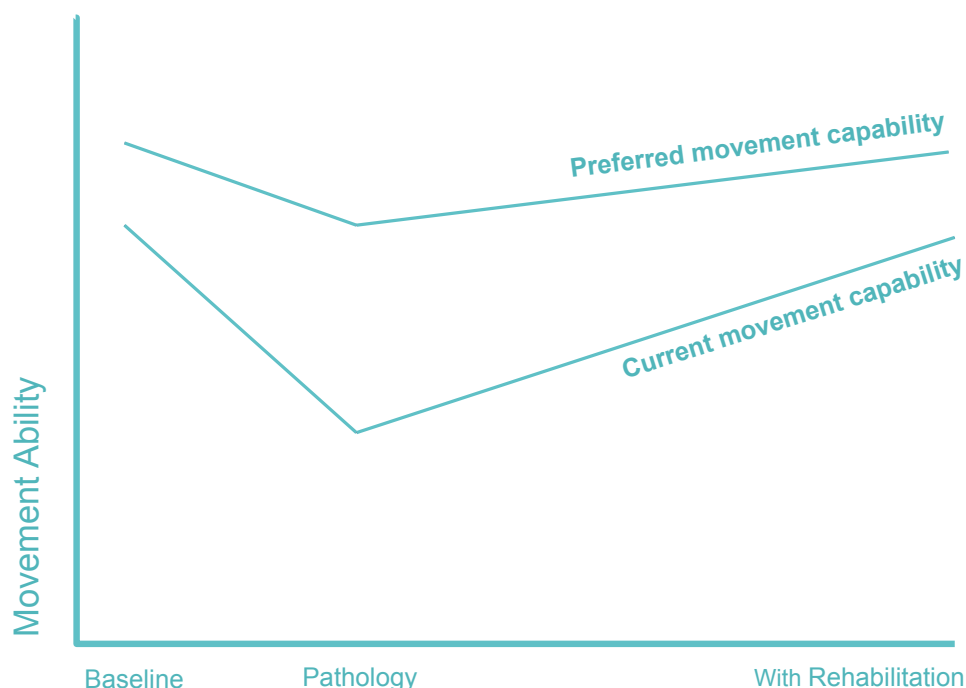


Figure 3. Graph of the Movement Continuum Theory (MCT) from Allen et al (37) reprinted with permission from the publisher Taylor & Francis Ltd (<http://www.informaworld.com>)

2.6 OVERVIEW OF THE RESEARCH FIELD

The following overview is structured in three main headings based on the three different study designs and specific topics represented in the three clinical studies forming this thesis.

2.6.1 Preoperative risk stratification and postoperative outcomes

Complication rates reported in the literature after abdominal cancer surgery differ widely due to various definitions and assessment methods. In Sweden, one in four (27%) undergoing elective colon surgery and almost half undergoing rectal (40%) or pancreatic (44–48%) surgery suffer postoperative complications (23, 24). In geriatric oncology the rates are slightly higher (38), and postoperative complications delay functional recovery (39). Both person-related as well as procedure-related factors such as duration of surgery, surgical site and approach, and anesthesia are important. Chronological age and type of cancer are examples of non-modifiable risk factors. Conversely, physical and respiratory performances are modifiable factors. Several sources have emphasized the importance of sufficient preoperative risk screening not only involving the conventional risk factors (for example gender, cardiopulmonary morbidity, smoking, and surgery-related factors), but also e.g. physical function, cognitive function and nutritional status in older adults (38, 40, 41).

Existing literature on the association between preoperative physical function in daily activities and different postoperative outcomes is extensive. However, there is a wide variability in assessment methods and outcomes, as well as target populations, and thus reported results. Studies targeting older adults undergoing abdominal surgery have mainly used CGAs (17, 38). Nevertheless, the physical domain of the CGAs often (but not always) consists of subjective measurements estimated by the patient or health care personnel, such as instrumental activities of daily living (IADL) or ADL. It is questionable whether ADL-measures are sensitive enough to represent physical performance. A scoping review summarized that in most cohorts within geriatric oncology, reduced ADL/IADL could not predict adverse postoperative outcomes (17). In contrast, some studies have shown the opposite (42).

When comparing different approaches to assess functional capacity to forecast mortality and cardiac complications after major surgery, patient-reported capacity with the Duke Activity Status Index (DASI) showed to be the most predictive compared to a subjective assessment by a clinician or a cardiopulmonary exercise test (CPET) (43). The CPET (the gold standard for assessing physical capacity) was superior in predicting other complications. There was a low-moderate ($r=0.43$) correlation between DASI and CPET (43). This indicates that functional capacity should not only be subjectively assessed by health care professionals, but should consist of both self-reported (by the patient) and objective measurements (44). An easy screening measure of physical performance would be preferable to add to CGAs or conventional preoperative risk assessments within geriatric oncology. Furthermore, a battery of physical assessments in high-risk individuals can be used to prescribe, monitor, and progress individual exercise (45).

2.6.1.1 Preoperative physical performance and postoperative outcomes

Some studies have shown that better physical performance, assessed with a single objective measurement such as the Timed Up and Go, and the incremental Shuttle Walk Test, is associated with a lower risk of postoperative complications in abdominal surgery (46-48). In contrast, a study using the Short Physical Performance Battery prior to pancreatic surgery reported that a better physical performance was not associated with lower odds of major complications or length of stay (LoS), but with discharge to a rehabilitation facility (49). In addition, there is evidence that reduced cardiopulmonary capacity measured by a CPET is a predictor for adverse postoperative outcomes (50). Nevertheless, it may not be feasible as a routine assessment in daily clinical practice. For an older population, submaximal functional assessments such as a six-minute walk test or a step test might be more suitable.

After abdominal cancer surgery, people ≥ 85 years are more likely to be discharged to nursing or rehabilitation facilities than those < 65 years. However, behind that association is a complex relationship between chronological age, functional status (ability to perform daily activities for basic needs), and postoperative complications (51). Furthermore, a prolonged LoS and other discharge destination than home were linked to a higher risk of readmission (52). Sacks et al. (53) reported that a higher age, poor functional status, and complications were associated with increased odds of discharge to post-acute care. Similarly, Robinson et al. (54) showed that a slow Timed Up and Go and dependence in ADL were associated with discharge to institutional care.

2.6.1.2 Preoperative performance and postoperative mobility

Early on it was shown that undergoing surgery corresponds to a 5–50% reduction in physiological and functional capacity as a cause of surgical stress (55). However, this was in the 1980s and surgical techniques, anesthetic management, and postoperative care have since changed. Moreover, 5–34% were reported after abdominal surgery also 20 years later (56). One reason for this might be that older adults more often undergo surgery today. Impairments in postoperative mobility can result in delirium, thromboembolism, pulmonary and/or surgical infections (2). Postoperative mobility is very important for the older individual in maintaining independence. Loss of functional independence on discharge from the hospital is associated with readmission, morbidity, and mortality (57). Regarding patient-related discharge criteria, pain control and the ability to mobilize independently take the longest to attain after colorectal cancer surgery (58).

Previous literature examining short-term postoperative physical function or performance is scarce (56, 59, 60). Hara et al. (59) investigated perioperative changes in walking distance in a gastrointestinal cancer cohort, which had declined significantly at postoperative day 10 but recovered to baseline levels at day 28. Another study showed that preoperative comorbidities, lower functional capacity and higher fatigue were associated with slower time to recover physically in older adults after colorectal surgery (60). The highest risk of adverse outcomes appears in the first postoperative period, which might be a time-point to investigate further.

2.6.1.3 Patient-reported recovery

Patient-reported outcome measures (PROMs) such as patient-reported recovery and health-related quality of life (HRQoL) are emerging in surgical care and in research as a measure of quality of care. It has been debated that the surgical community needs to incorporate outcomes of importance to the patients, in addition to disease and health-care focused outcomes (61, 62). Patient-reported recovery is paramount as postoperative length of stay in the hospital is getting shorter and being discharged from the hospital is not equal to being recovered. In a qualitative analysis, concepts of recovery described by patients were: energy level, pain control, physical endurance, and being able to perform daily routines (63).

Nevertheless, the multifactorial aspect of patient-reported recovery creates a complexity (64), and PROMs previously used within the context have limited psychometric evidence such as reliability (65). Measurements of patient-reported recovery need to be further developed, and patient-reported outcomes need to be added to evaluations of preoperative interventions in addition to objective measures such as physical performance (62). We cannot rely solely on one dimension of outcome measures, but must combine measurements on the micro and meso levels, which are important to both the patient and the health care system.

2.6.2 Prehabilitation and preoperative physical exercise

Prehabilitation, defined as “enhancing functional capacity of the individual to enable them to withstand an upcoming stressor” (33), is an emerging field of research worldwide. The umbrella concept often consists of three domains: physical, nutritional, and psychological optimization. Recently, lifestyle changes (such as smoking cessation) have also been addressed (66), and additional optimization of comorbidities by a nonsurgical clinician show the potential to reduce postoperative complications (67). The importance of a multimodal approach, including the previously described domains, within the surgical field has been emphasized (68). In contrast, recent RCTs that have shown potential effects on postoperative complications are unimodal in their approach, only including physical exercise (69, 70).

Physical activity is defined as “any bodily movement produced by skeletal muscles that result in energy expenditure,” and physical exercise as “planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness (71).” Thus, physical exercise is a part of the concept of physical activity. In the physical domain of prehabilitation, which is the focus of this thesis, exercise plays a major role. This is based on the hypothesis that optimization of physical fitness can contribute to minimizing the risks associated with surgical treatment, given that physical activity in general has positive effects on the cardiorespiratory, musculoskeletal, and immune systems in older adults (72).

2.6.2.1 Exercise physiology in older adults

Physical activity has the same benefits on older adults in terms of body composition and cardiorespiratory capacity as on younger people (73, 74). In addition, in the preoperative

context it has previously been shown that the lower the physical capacity to start with, the greater the gain (75). Exercise prescriptions need to be specific, include progression, and take the current health and physical capacity of each individual into account (73, 76).

The benefits of physical exercise are transferable to everyday mobility and independence (77, 78). The change in body composition as a part of physiological aging incorporates increased body fat and loss of muscle mass (sarcopenia), which can result in reduced physical function (73). Older adults lose muscle power (muscle contraction x velocity) more rapidly than muscle strength, probably due to a reduction in type II fibers (78). Aerobic exercise can improve cardiopulmonary capacity by increasing heart rate variability, reduce arterial stiffness and inflammatory markers, improve cardiac output, and improve gas exchange and vascularization. Resistance training can improve muscle strength and power, increase fat free mass and basal metabolic rate, as well as improve insulin sensitivity (72).

Age-related reductions in cardiorespiratory capacity and strength indicate that older adults need to use a higher proportion of their maximal capacity even at lower exercise loads compared to their younger counterparts (73). Heart rate is often used as an indicator of exercise intensity. Physical exercise can improve resting heart rate but not maximum heart rate, which is age-dependent (79). It must be remembered that the maximal heart rate decreases with increasing age, and medications such as beta-blockers as well as comorbidities such as cardiopulmonary disease will further affect heart rate. This limits the ability to compare heart rate with subjective perceived exertion. In regards to rating scales of perceived exertion, the Borg CR-10 scale, with fewer steps, is suggested to be more suitable for older adults than the RPE scale, which is correlated to heart rate in younger people (80, 81).

2.6.2.2 Exercise and cancer

In cancer populations, benefits of physical exercise have been seen on cancer-related fatigue, functional capacity and quality of life (82, 83). It is important to adapt the exercise to possible disease- or treatment-related symptoms, as well as contextual factors such as personal and environmental factors (45). Furthermore, a safety reference guide including ranges for blood values, cardiorespiratory symptoms, and physical function has been proposed (84). For example, a hemoglobin concentration >100 g/L indicates that exercise is tolerated, but lower values need to incorporate monitoring of symptoms and adjustment of exercise dose, and a concentration <80 g/L can be considered a contraindication.

Many exercise programs within oncology range between 4 and 16 weeks, and exercise prescriptions are based on the exercise principles of specificity, progressive overload, individualization, and recovery with some modifications (85). The exercise prescription needs to be adapted to the individual's current physical status to reduce the risk of under or overdosing (45). Cancer cachexia can be evident in cancer patients, and is defined as "a syndrome characterized by an ongoing loss of skeletal muscle mass, with or without a loss of fat mass, leading to progressive functional impairment (86)." Physical exercise has the potential to help optimize patients with cancer cachexia by improving muscle protein

synthesis, reduce catabolism, and regulate levels of inflammation. However, further studies are needed regarding exercise dose, safety and cachexia as a specific outcome (86).

2.6.2.3 Preoperative exercise prior to abdominal surgery

Multiple studies have investigated preoperative exercise prior to oncological and major abdominal surgery. Consequently, numerous systematic reviews have been published, with the majority between 2014 and 2019 (87-93). Today, evidence exists that preoperative physical exercise can increase functional and physical capacity (94-96). However, there are still knowledge gaps regarding optimal interventions types, doses and settings for different surgical populations (regarding pathology, preoperative time frames, and age groups), as well as robust evidence of effects on postoperative outcomes (87, 88). This is probably because most studies include low-risk patients and are small-scaled, increasing the risk of type II error. In addition, there is heterogeneity in endpoints and interventional content, with a handful of studies steering the results. To date there are only a few adequately powered trials showing the potential to reduce postoperative complications (69, 70). In 2018, the first clinical guideline on the topic was published to guide patient selection and practical exercise principles (96), and recruitment is on-going in numerous RCTs registered in clinical trial databases. Hopefully, the area will keep progressing in the coming years to provide a solid evidence base in research and in the clinic to elaborate on the implementation phase.

2.6.2.4 Preoperative exercise in high-risk patients within a limited timeframe

Preoperative exercise in older adults undergoing abdominal cancer surgery is not as well explored. Most published studies include patients with a mean or median age up to 70 years. Given the lack of studies that include older adults with low functional capacity, the evidence of effectiveness in preoperative exercise is low in multiple surgical fields (8, 97, 98). Prior to colorectal cancer surgery, benefits of functional physical capacity have been reported but no effects on postoperative outcomes have been shown (99, 100). In a study including high-risk patients undergoing abdominal surgery, defined as over age 70 and/or an American Society of Anesthesiologists (ASA) score of 3–4 (69), preoperative exercise reduced postoperative complications. However, the intervention time was 6 weeks, which is longer than the time period in the Swedish context in relation to standardized care procedures.

Specific cancer prehabilitation is defined as “a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment...”, adding the time-limiting component (101). In Sweden, the time frame from treatment decision to date of surgery for colorectal cancer can be as short as 2–3 weeks. Preoperative inspiratory muscle training increases maximal inspiratory pressure (MIP) and has shown the potential to reduce postoperative pulmonary complications (PPCs) such as pneumonia in only 2 weeks (89, 102). Little is known about the short-term effects of aerobic and strength training as most studies have been for at least 4 weeks. In recent years there have been trends towards high-intensity exercise given the short time windows (103). This has been proven effective within cardiovascular studies (104), but not yet in cancer populations.

In addition, interventions involving older adults should focus on improving outcomes important to the older individual, whereas functional training, training that has a meaning to maintain or improve performance of a specific goal or task in daily life, is implied (105, 106). As surgery affects multiple organ systems, we need to involve multiple exercise domains in the interventions, such as inspiratory muscle training (IMT), strength training, and aerobic training. Furthermore, the programs need to be tailored to comorbidities.

2.6.2.5 Intervention setting and compliance

Exercise interventions can be considered time-consuming and demanding. In studies of preoperative optimization prior to colorectal resections, compliance with the interventions ranges from 16 to 98% (107). In previous literature, the concepts compliance and adherence have sometimes been used interchangeably. To clarify, in this thesis we investigated compliance with the exercise intervention, defined as the extent to which the participants complete the number of planned sessions. Adherence is more about to what extent the dose of the prescription is reached and if it is being maintained (108). It has been suggested that compliance of older adults, is generally higher in supervised programs (109). Advantages of home-based exercise for older adults include minimized transportation issues, and that the older individuals get to exercise in their habitual environment (110). In previous studies, home-based exercise is mainly self-administered, which differs from combining it with home-based supervised exercise. Supervision can be time-consuming and costly in terms of resources. Nevertheless, supervision may be essential for safety purposes and appropriate exercise progression in the home setting when conducting physical exercise at the high estimated exertion levels in older adults (111).

Center-based intervention might be preferable as it provides social contact with other patients in the same context, and one possibility for overcoming transportation issues is to conduct the exercises in primary care centers, i.e. closer to the patient. In Sweden the government's long-term focus on cancer care indicates that primary care plays a key role in contributing to coherent care chains in connection with the discovery of cancer, follow-up, and rehabilitation after completed treatment. Therefore, they suggest that knowledge of cancer and cancer rehabilitation need to be strengthened in primary care (112).

2.6.3 Attitudes toward and perceptions of preoperative physical exercise

Challenges such as recruitment issues and selection bias in studies that include preoperative exercise make it crucial to go beyond clinical measures to add sufficient knowledge to the research field: the patient's perspective. This raises the questions of how we can modify exercise interventions to facilitate participation. In addition, in cancer surgery, time restraints from treatment decision to surgery are apparent. Even though it has been suggested that surgery delay is not associated with a worse outcome regarding survival in colon cancer patients (113), more high-quality evidence on the effects of preoperative exercise and optimization is required to modify the preoperative time frame in clinical practice (114). Consequently, it is important to determine if there is more than one possible pathway.

Patients express a need for substantial information, communication, and regular appointments with health care throughout the preoperative period, sometimes regardless of the length of waiting time (115, 116). In a study investigating experiences with a 12-week exercise program before cardiac surgery, informants perceived the exercise as valuable for increasing exercise capacity and reduce anxiety (117). The transferability to a surgical cancer population should be considered with caution given the differences in the preoperative process and the absence of malignancy. In another study exploring quality of life (QoL) during preoperative exercise in rectal cancer the participants reported a positive effect on QoL and a feeling of control at an otherwise demanding time (118). In both studies, the informants participated in the exercise program whereas information from declining patients is still missing.

3 RATIONALE

The incidence of abdominal cancers increases with advancing age, and the mean age at diagnosis for colon, rectal, liver, and pancreatic cancer, is high. Existing literature includes study populations from the age of 18, therefore the population in focus in the present thesis is ≥ 70 years of age. Adding objective functional assessments of physical performance to existing preoperative screening can provide information to identify older adults with vulnerability that are at risk of adverse postoperative outcomes and in need of preoperative optimization. In addition, short-term physical decline and patient-reported recovery is of utmost importance for postoperative independence. Information regarding this topic is still sparse in older adults undergoing abdominal cancer surgery.

Regarding preoperative exercise, there are still challenges in recruiting older adults, and further research is needed to identify the optimal intervention type, duration, and intensity of exercise (as this group is not as well explored). To put the older individual in focus, and possibly increase compliance, we designed a home-based intervention supervised by physical therapists in primary care to allocate resources close to the older adult and their habitual environment. In addition, we included several exercise modalities to target organ systems of the whole body, and made it functional and possible to tailor to comorbidities. Furthermore, there are time constraints in preoperative cancer care to consider. There is evidence that 4–8 weeks of preoperative exercise is sufficient to see an effect on functional physical capacity, but not yet for shorter interventions. For this reason, more research on the feasibility and effects of short-term exercise interventions is necessary given the current preoperative time span in onco-surgical clinical practice. We also need to dig deeper into the patients' own perspective, which has commonly been overlooked compared to outcomes of importance to health care.

All of the above lie within the expertise of physical therapy, to assess and provide interventions, which aims to address and improve reserve capacity for the older population.

4 AIMS OF THE THESIS

Overall aim

This thesis aims to determine how preoperative physical performance is associated with postoperative outcomes, and to increase knowledge regarding supervised home-based physical exercise as a potential intervention prior to abdominal cancer surgery in older adults.

Specific aims of the papers

- I** To examine the association between preoperative physical performance and activity, and severity of postoperative complications, length of stay, and discharge destination in people ≥ 70 years of age after abdominal cancer surgery
- II** To describe the short-term changes and study the associations between preoperative physical performance and postoperative mobility, as well as patient-reported recovery in people ≥ 70 years of age undergoing abdominal cancer surgery
- III** To evaluate the feasibility of a preoperative, supervised home-based physical exercise program in people ≥ 70 years of age undergoing colorectal cancer surgery
- IV** To describe older patients' attitudes towards, and perceptions of, physical activity and exercise when scheduled for colorectal cancer surgery

5 MATERIALS & METHODS

5.1 STUDY DESIGNS

The thesis consists of three clinical studies, resulting in four research papers, with diverse study designs (an overview is presented in table 1). All studies were performed in Stockholm County. **Study A** is a **prospective observational cohort study** conducted at two hospitals (three sites) between December 2015 and 2017, and the first two papers of the thesis are based on this material. **Study B** is a single-center **feasibility study with a randomized control design**, and **study C** is a **qualitative study** involving semi-structured interviews. The feasibility study of the interventional design ranged from October 2016 until June 2018. Lastly, the interview study was initiated in 2018 and finalized at the end of the same year.

The methodological approach and process of this thesis corresponds to **the public health model** (119) seen as a continuum where this thesis involves the first three steps and then continues into the following parts of the overall project (figure 4). The model runs from identification to implementation.

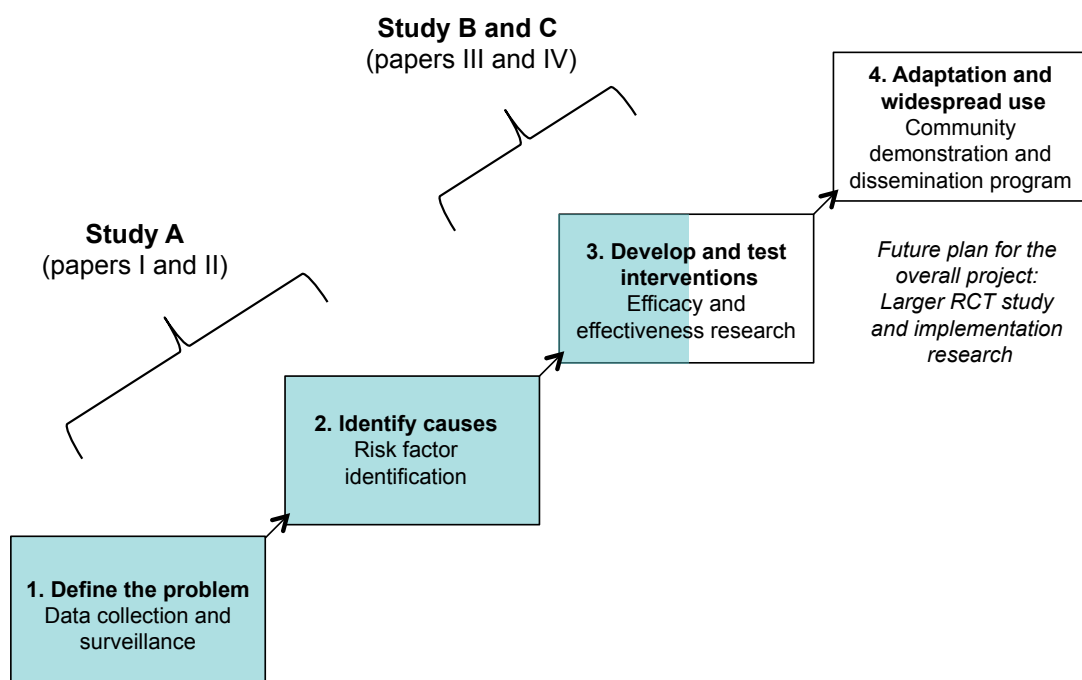


Figure 4. The current thesis incorporated in the Public Health Model. Adapted from Sleet DA, Hopkins KN, Olson SJ. From discovery to delivery: injury prevention at the CDC. Health Promot Pract 2003;4:98-102, and used by permission from SAGE Ltd.

5.1.1 Considerations regarding study designs in studies A, B, C

Regarding the epidemiological design of study A, which includes analyses of association in a defined condition and population, the effect of bias in epidemiology needs to be addressed. First, a statistically significant association does not mean a causal relationship (120). Our aim was to investigate the association between an explanatory variable, an outcome, and multiple components involved in each association. Therefore, we initially chose our covariates (confounders, mediators, or interaction variables) for the different models based on clinical reasoning and the scientific literature, then tested them statistically. Second, non-participation, which is difficult to avoid as patients' participation in research studies is voluntary, should be described and discussed as it impacts generalizability. One way to address this is by comparing participants and non-participants using available information such as age, and gender. In addition, the reasons for declining or exclusion from a study should be evaluated regarding loss at random or by choice causing selection bias (121). In the preoperative context, there is already a risk of pre-selection prior to surgery, and more health-conscious patients tend to participate in studies involving physical assessments and exercise. Third, dichotomization or categorizations of outcomes, and the use of cut-offs may cause measurement error in the form of misclassification. However, it may be preferable to make clinical interpretations of the findings easier. The reporting of findings in papers I and II were structured according to the STROBE guideline for observational studies (122).

For study B, the methodological design was based on Thabane et al. 2010 (123) to investigate process feasibility as a primary endpoint and scientific feasibility as a secondary endpoint. A feasibility study aims to answer "whether something can be done, should we proceed with it, and if so, how" (124). It can help identify modifications and improvements for a definitive trial, or even dissuade conducting a larger resource-demanding trial (125). Considering the complexity of the study procedures and interventions in preoperative exercise trials, it is important to evaluate feasibility aspects prior to a full-scale trial (126). One disadvantage mentioned with the feasibility design is a limited external validity (127). Selection bias sometimes occurs in exercise studies targeting vulnerable older people when the fittest individuals participate and the most unfit decline. Another criticism of feasibility studies is that they take time and they incur costs prior to a definitive trial of efficacy and/or effectiveness (125). Nevertheless, changes provided from lessons learned in a feasibility study aim to improve the definitive trial and reduce the risk of initiating a trial that might not prove to be feasible. Findings were reported in accordance with the extended CONSORT statement for pilot and feasibility trials, as well as the TIDier checklist (128, 129).

A qualitative approach for study C was chosen during the on-going recruitment process of the interventional feasibility study, to enable a deeper understanding of the patients' attitudes and perceptions of the topic (130, 131). An inductive content analysis was applied as the research question was not theory driven and as there was limited research exploring the topic of interest qualitatively. The analytic procedure was conducted according to Elo & Kyngäs 2008 (132), trying to reduce interpretation and stay close to the text material in the initial steps of the analyses and then incorporating some interpretation later on in the

findings. Reporting of the findings was based on the COREQ checklist for reporting qualitative research (133).

Table 1. Overview of the included studies and papers in the thesis

Study	A		B	C
Paper	I	II	III	IV
Study design	Prospective cohort study	Prospective cohort study	Feasibility study of RCT design	Qualitative interview study
Data collection	Preoperative: - Walking distance - Functional leg strength - Grip strength - Gait speed - MIP - Self-reported physical activity Postoperative: - Complications (Clavien-Dindo) - LoS - Discharge destination	Preoperative and on discharge: - Walking distance - Functional leg strength - Grip strength - Gait speed - MIP On discharge: - Patient-reported recovery	- Screening lists of the recruitment process - Registration of compliance to the exercise - Surveys on participant and instructor acceptability - Registration of adverse events - Registration of dose level and response (walking distance, functional leg strength, gait speed, and MIP)	Semi-structured individual interviews (face-to-face or by phone)—audio-recorded and transcribed.
Inclusion period	December 2015 to December 2017		October 2016 to June 2018	2018
Participants, n	≥ 70 years of age undergoing abdominal cancer surgery n=197		≥ 70 years of age undergoing colorectal cancer surgery n=23	
Outcomes	Primary: (Severity of) postoperative complications Secondary: LoS, and discharge destination	Primary: Physical decline, and postoperative mobility Secondary: Patient-reported recovery	Primary: Process feasibility (recruitment, compliance, and acceptability) Secondary: Scientific feasibility (exercise dose, safety, variance of treatment effect on physical performance)	From transcripts to overarching theme
Data analysis	Ordinal logistic regression, median regression, and multinomial logistic regression	Logistic and ordinal logistic regression	Descriptive statistics (median, IQR, range), ANOVA and 95% CI, effect size (the probabilistic index)	Inductive content analysis according to Elo & Kyngäs 2008 (132)

Abbreviations: RCT=Randomized controlled trial, LoS=Length of stay, MIP=Maximal Inspiratory Pressure, IQR=Interquartile range, ANOVA=Analysis of Variance, CI=Confidence Interval

5.2 PARTICIPANTS AND CONTEXT

All phases (screening, recruitment, and assessments) of the three studies were conducted in a clinical hospital setting, in surgical offices and surgical wards. Karolinska University Hospital is a large-scale hospital located in two geographic sites in the north and south of Stockholm. Stockholm South General hospital (Södersjukhuset) is an emergency hospital located in central Stockholm with a focus on chronic diseases, and Ersta hospital is a smaller hospital located in central Stockholm. In addition, the intervention in study B was performed in the participants' homes with physical therapists from home-rehabilitation units in primary care, adding primary care and the home settings as arenas for physical exercise. Some of the interviews in study C were also conducted in the participants' homes.

For study A, patients ≥ 70 years, undergoing abdominal surgery due to verified or suspected colon, rectal, liver, biliary tract, pancreatic cancer, or liver metastases, were eligible. Regarding liver surgery, there is heterogeneity in the magnitude of surgical procedures between e.g. surgery due to metastases or primary tumor. However, the individual differences between patients are thought to be greater than the differences in surgical approaches so these patients were grouped together. For studies B and C, patients ≥ 70 years undergoing abdominal surgery due to verified or suspected colon or rectal cancer were eligible. This was done because abdominal surgery is considered a high-risk surgery and the mean age at diagnosis is high (72 years). We excluded other abdominal cancers such as pancreatic and gastric cancer from this study due to the differences in preoperative pathways between the cancer diagnoses. Consequently, other studies are needed to examine those types of cancer in particular. In study C, the same study context as for study B was chosen, as the aim was to describe attitudes toward preoperative physical exercise in the same target population and inclusion criteria. Accordingly, the participants in study C were considered eligible for the exercise intervention.

5.3 DATA COLLECTION

5.3.1 Workflow and procedures

For study A, patients from 70 years of age and older scheduled for abdominal cancer surgery at Stockholm South General hospital and Karolinska University hospital were approached at their first visit to the surgical office and asked to participate in the study. For the participants, baseline assessments regarding physical performance were conducted and questionnaire data, as well as clinical data were collected prior to surgery (one week or the day before hospital admission). Demographic and surgical-related data were retrieved from the medical records. The assessments of physical performance were repeated on discharge from the hospital. In addition patient-reported recovery was collected at postoperative day 4 and at discharge, and postoperative delirium was screened for at day 4 with the Confusion Assessment Method (described on page 22) (134). Data on postoperative complications within 30 days after

surgery, mortality, length of stay, and discharge destination were collected from the medical records during the postoperative period (figure 5).

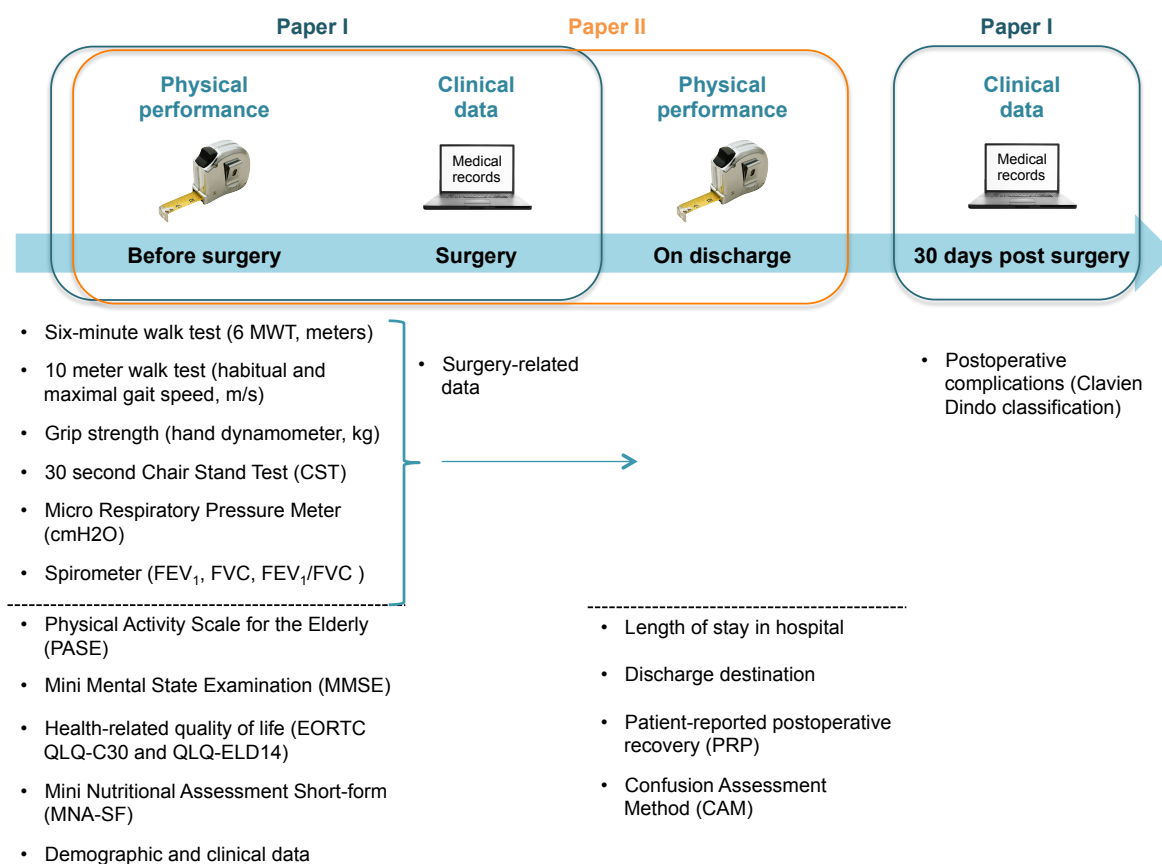


Figure 5. Overview of data collection in study A (including paper I and II). Abbreviations: FEV₁=Forced Expiratory Volume in 1 second, FVC=Functional Vital Capacity, EORTC= European Organization for Research and Treatment of Cancer

For study B, patients ≥ 70 years of age scheduled for colorectal cancer surgery at Stockholm South General hospital were approached for participation. After inclusion, the participants were randomized to the intervention group (supervised physical exercise in the home setting) or standard care group. Randomization with a 1:1 allocation ratio was conducted by a study coordinator, separate from the assessments and intervention, from a web-based spreadsheet and was performed at inclusion and collection of informed consent to enable planning of surgical date. Each study participant was informed of his or her group allocation after the first assessment. The assessors were blinded to the group allocation throughout the (single-blinded) study. Preoperative physical performance (same assessments as in study A) was tested at baseline, prior to surgery, and close to discharge from the hospital (figure 6). The assessors and the training physical therapists had no contact during the study.

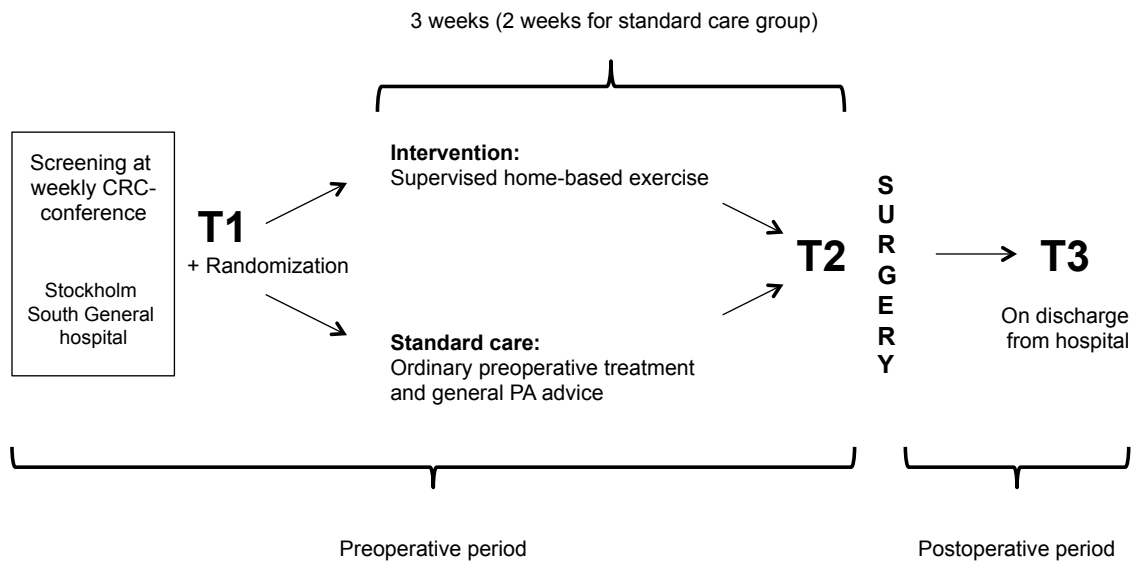


Figure 6. Summarized study flow of study B (paper III). Abbreviations: CRC=Colorectal conference, PA=Physical activity, T1=Baseline test of physical performance, T2=Pre-surgery/post-intervention test of physical performance, T3=Postoperative test of physical performance

For study C, patients with the same profile, i.e. eligible for a preoperative exercise intervention as in study B, were approached for participation when scheduled for colorectal cancer surgery at Karolinska University hospital in Solna and Ersta hospital. An individual interview was conducted, face-to-face at the participant's home, at the ward or by phone, before surgery but at the end of the preoperative period. Self-reported physical activity level was collected after the interview with the PASE questionnaire (135).

5.3.2 Measurements

5.3.2.1 Physical performance

In consideration of the study population, the chosen instruments need to take the functional aspects into account to be able to detect and evaluate components that are central to coping in everyday life (136, 137). Objective measurements such as gait speed and chair stands give an indication of what they can really perform (138) compared to self-assessed, which is a subjective estimation.

As most activities of daily living are performed at submaximal levels of exertion, functional capacity was assessed with the **Six-minute walk test** (6 MWT), walking back and forth as many laps as possible over a 30-meter distance for 6 minutes (139). The number of meters, self-reported effort and dyspnea (Borg CR-10 scale), and oxygen saturation with a pulseoximeter were recorded at the end of the test. The 6 MWT is a responsive outcome

measure for the study population and preoperative context (140). The CPET is considered the gold standard for assessing physical capacity (50). However, it is not always functional for older adults, nor feasible in the clinical everyday setting as it is resource consuming. The 6 MWT has been suggested as an adequate substitute when CPET is unavailable (141, 142).

Habitual and maximal **gait speed** were measured over a 10-meter distance with a 2-meter acceleration and deceleration phase and timed by the study assessor with a stopwatch. The participant was asked to walk the distance twice, first in their habitual speed and second as fast as they could without running. The test is valid and reliable for older adults, and it has previously been implied that conducting both habitual and maximal gait speed gives a fuller picture of the patient's capacity (143). Habitual gait speed may be related to an overall functional status, whereas maximal gait speed is related to a person's fitness and ability to cope in the community (143, 144). As the test is assessed over a short distance, it does not incorporate an endurance component as compared to the 6 MWT.

Upper-extremity strength was assessed via **handgrip strength** with the JAMAR handheld dynamometer (Lafayette Instrument Company, Lafayette, Indiana, USA) in a sitting position with no support for elbows and registered as kilograms (kg). Each test was repeated three times per hand to ensure consistency, and the highest value of the dominant hand was used in statistical calculations. Handgrip strength is a measurement of maximal muscle strength in hand and forearm, and is associated with several health outcomes such as general muscle strength, mortality, and hospital length of stay (145).

Functional leg strength was assessed with the number of chair-stands performed over 30 seconds as described by Jones et al. (146) from a chair without support from the arms. The test is valid for older community-dwelling adults and is suggested to be a valid proxy for lower-extremity strength (146). The time-related version of the test was chosen to eliminate floor effects, which can occur in older adults performing CST with an absolute number of sit-to-stand repetitions. Functional leg strength incorporates large muscle groups and is of clinical importance for mobility and independence in daily activities.

For **maximal inspiratory muscle strength** (MIP) a respiratory pressure meter (MicroRPM, Care Fusion, San Diego, California, USA) was used. The test was conducted in a sitting position, with a maximal expiration before the test (147). It was performed three times or more until the discrepancy between the two highest values was no more than 10%. A poor test performance may result in a misleadingly low value (148).

Lung function, Forced Expiratory Volume 1 sec (FEV_1), Forced Vital Capacity (FVC) and FEV_1/FVC , was measured with a spirometer (MicroLoop Micro Medical; Chatham, Kent, UK) to be able to describe the respiratory function of the participants in study A and B given that lung function can affect the results of other performance tests.

5.3.2.2 Questionnaires

The participants reported their preoperative **physical activity level** with Physical Activity for the Elderly Scale (PASE), which they completed in their home. PASE is validated for the age group, where the majority is no longer working for pay (135). The score ranges from 0–400 or more, depending on item 10 in the questionnaire, which involves a free text answer regarding voluntary work. A lower score is equal to a lower self-reported physical activity. Physical activity can differ during the year due to weather conditions, the season of data collection was therefore examined as a confounder in the regression models of study A. As a downside, the PASE score cannot easily be converted into METS reducing comparability to other physical activity surveys used in similar studies.

Cognitive function was measured with the Mini Mental State Examination (MMSE) (149) for comparative data to detect any postoperative delirium. The MMSE has previously been used in older surgical populations (150). Postoperatively the Confusion Assessment Method (CAM), an easy administrative assessment containing nine criteria, was performed to detect possible postoperative delirium (134). It has been validated within general and geriatric medicine, but has shown to be less sensitive in detecting postoperative delirium after cardiac surgery (134, 151). Postoperative delirium, manifested as an acute change in cognitive status, mainly occurs early on after surgery but can have long-term consequences (152).

Health-related quality of life was measured with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire and the QLQ-ELD14 specific for the older cancer population in studies A and B (153, 154). Each question has a four-grade answer, and the scale and single-item scores ranges from 0–100. The QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, nausea), a seven-grade global health status/QoL scale and single items (dyspnea, loss of appetite, insomnia, constipation and diarrhea, financial impact of the disease). A high score on the functional scales and the QoL scale indicates a high level of functioning and a high QoL, unlike the symptom items where a high score indicates more severe symptoms. The QLQ-ELD14 consists of five scales (mobility, worries about others, worries, maintaining purpose, and burden of illness) and two single items (joint stiffness, and family support). High scores indicate poor mobility, much worry, high burden and stiffness, on the contrary high scores also indicate good maintenance and family support (154).

Comorbidities were registered with the Charlson Comorbidity Index (155). The index consists of 19 conditions weighted (from 1–6) according to the strength of their association with 1-year mortality. Age can be taken into account in the index score; in the present study we chose to adjust for age in the regression models instead. As the index is validated for detecting risk of mortality based on comorbidities (155), the index does not consider comorbidities related to outcomes other than mortality (such as disability), which is a disadvantage (156).

We screened for preoperative nutritional status with the **Mini Nutritional Assessment Short-form (MNA-SF)** (157). The MNA-SF is a shorter version of the full MNA to make it feasible as a fast screening tool in the clinical setting. The scoring sheet includes six questions regarding change in diet intake and weight loss the last three months, mobility, acute disease, neuropsychological problems, and Body Mass Index. The items are scored from zero to two or three and the total score is categorized as “normal nutritional status,” “risk of malnutrition,” or “malnourished.” It has been validated in the older population (158). Nevertheless, it is recommended that a full MNA is provided for malnourished individuals (159). A limitation of the MNA-SF is that specificity is low and sensitivity is high, leading to an overestimation of malnutrition (160). However, this may be better than individuals being misclassified as well-nourished when in fact they are malnourished.

5.3.2.3 Outcomes

Postoperative morbidity was reported as **postoperative complications** and registered with the Clavien-Dindo classification (161). Clavien-Dindo consists of an ordered ranking scale according to the severity of complications from grade I, equal to “any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions,” to grade V, equal to “death of a patient,” and divided into 5 categories of complications (infectious, cardiovascular, neurological, surgical, and others). The classification is frequently used in clinical practice as well as in quality registers in Sweden. However, only the most severe complication in each individual is taken into account, which is a disadvantage of the ordered ranking scale. A comprehensive complication index (CCI) based on the Clavien-Dindo was developed enabling a cumulative complication burden in a linear scale from “0=no complication” to “100=death” (162). Postoperative morbidity is a burden for the individual as well as costly and resource consuming for health care by, for example, increasing in-hospital treatment and LoS.

When **length of stay in hospital (LoS)** is used as an outcome, external factors such as available beds in a rehabilitation unit can delay discharge. Therefore, we defined LoS as readiness for discharge, i.e. when the referral to a rehabilitation unit was sent or when the patient was ready to go directly home based on mobility, medical stability, and pain control. A similar approach was previously described in patients with colorectal cancer (163). As different surgical groups have various median LoS, we controlled for cancer type and surgical approach in the multivariable analyses of paper I.

Being able to return home instead of being referred to further care after a hospital stay is an important patient-centered measure, and reduces health care costs. Consequently, it has an effect on both the micro and meso levels. The outcome **discharge destination** was categorized into the destinations home, rehabilitation facility and further care such as, a geriatric clinic or residential care/nursing home. In Sweden, a somewhat adequate level of physical function is needed for referral to a rehabilitation unit, meaning that the population in the active rehabilitation setting is neither the fittest nor the most unfit.

Mobility, defined as “the ability to move without assistance,” is essential to perform activities in everyday life and to sustain independence. Both muscle strength and muscle power of the lower extremities are important components to enable mobility (78). Muscle mass attenuates faster in the lower extremities (73), and changes in muscle composition, reduced muscle quality and poorer contractile characteristics of the muscle fiber occur more frequently at older ages. We chose functional leg strength and ability to rise from a chair independently without support as a proxy for postoperative mobility, as we saw the greatest decline in this performance when comparing preoperative and postoperative values in this population and it is also a component of sarcopenia. The outcome was dichotomized into “independent rise” coded as 0, and “dependent rise” coded as 1.

We assessed **patient-reported postoperative recovery** with the postoperative recovery profile (PRP) (164). It consists of 19 items with four response alternatives of symptom severity ranging from “none” to “severe,” which covers five dimensions: physical symptoms, physical function, psychological, social, and activity. The participant was asked to fill in their current perception at the time the questionnaire was administered. For the in-hospital assessments we used the 17-item scale, which excludes two items regarding “re-establishing everyday life” and “sexual activity” (164). The PRP is recovery-specific and has good content validity, but on the downside lacks somewhat in reliability (65). When reporting our findings we used the global recovery scale where the number of “none” answers were summed up and categorized into the categories: fully recovered (17 “none” answers); almost fully recovered (13–16 “none” answers); partly recovered (8–12 “none” answers); slightly recovered (7 “none” answers); and not recovered at all (<7 “none” answers) (165).

Process feasibility as described by Thabane et al. 2010 (123) was undertaken to investigate feasibility of the process in study B. Variables addressed were: recruitment rate (defined as the number of participants enrolled from the eligible patients) including reasons for non-participation; compliance to the exercise intervention (defined as the number of planned sessions attended, a rate of > 80% was considered feasible (166)); and acceptability defined as the participants’ and instructors’ satisfaction retained from survey answers. The surveys contained 19 and 16 questions (seen in tables 2 and 3 in paper III), respectively. Regarding **scientific feasibility** (123), we described exercise dose, treatment safety as occurrence of adverse events, and estimated the variance of treatment effect on physical performance.

5.3.3 Intervention

The exercise regime incorporated several exercise modalities (74), with an overall functional approach (106). The exercises were intended to specifically train abilities and movement that will enhance a functional outcome, so the functionality of the exercise is dependent on the context in which the function is intended to be maintained or improved (105). The patient and user organizations Network Against Cancer and the Swedish Pensioners’ Association were included in discussions, and provided input regarding the design of the intervention. The intervention is described in more detail on pages 4 and 5 in paper III, and as a schematic

summary in figure 7. To increase intensity, short intervals (below 60 sec) were included in the aerobic exercise block, and weight belts were used in the functional strength training.

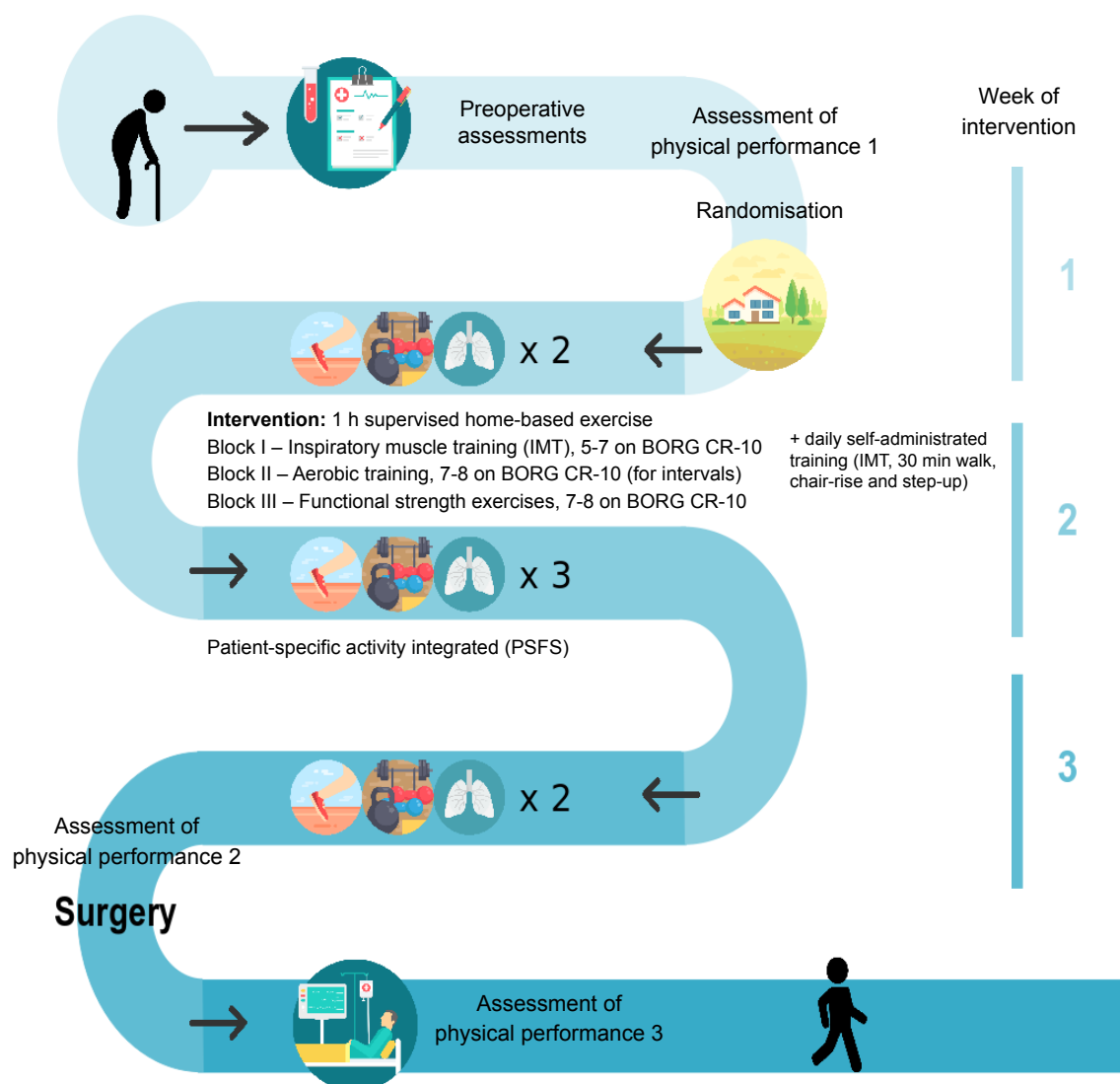


Figure 7. Infographic of the preoperative exercise intervention in study B. Icons made by [freepik, Roundicons, and Icon Pond] from www.flaticon.com

One to three patient-specific activities were incorporated into the exercise intervention, based on the Patient-Specific Functional Scale (PSFS) (167). It can be used as both an outcome measure and an identification tool. In study B we primarily used the PSFS as an identification tool to be able to include activities important to the individual into the exercise intervention. At the first visit in the participant's home, the participant described one to three activities they had difficulties performing, and graded the severity of the difficulties on a rating scale from 0 ("cannot perform the activity at all") to 10 ("can perform the activity without any restrictions").

Standard care was incorporated regarding the nutritional and psychological components for both study groups. For nutritional screening, the contact nurses used a standardized checklist at the patient's first visit to the surgical office. They screened for nutritional status with the following data collection (a modified Subjective Global Assessment–SGA): Weight, height, Body Mass Index, weight a year ago, diet intake the last month (compared to earlier), and possible barriers in diet intake. If a risk of malnutrition or manifest malnutrition were detected, a dietician was contacted for further assessment, individualized interventions such as nutritional supplements, and follow-up. Similarly, a counselor was contacted if the patient was in need of psychological or social support.

5.3.4 Interview

Semi-structured interviews were chosen due to the descriptive and novel nature of the research objective. Participants in study C were interviewed by a physical therapist or a nurse face-to-face in their home or in the surgical ward, or by telephone prior to colorectal cancer surgery. The interviews took place as close to the surgery as possible to enable the participant to describe their experience of as much as possible of the preoperative period. The interview was recorded with a Dictaphone and then transcribed verbatim, resulting in 17 interviews, each between 16–30 minutes, and 116 pages of text material. The interviewers used a study-specific interview guide, seen on page 6 of manuscript IV.

5.4 ANALYSIS

Papers I–III incorporated quantitative analyses and manuscript IV qualitative analyses. Papers I–III includes a variety of descriptive and inferential statistical methods, which can be viewed in table 2. In general, for all studies, mean and standard deviations were used to describe continuous variables that had normal distribution. The normality of continuous data was tested graphically and statistically using Q-Q plots and the Shapiro Wilks test. We handled the HRQoL data as continuous in the descriptive tables of papers I and II, for comparability with reference data. For missing values in the scales of the HRQoL questionnaires, imputation was conducted if a minimum of half the items of the scale had been answered (by taking the average of answered items) (168).

For categorical variables and skewed data, median and interquartile range (or range) were reported. Due to the small sample size in study B, non-parametric analyses were conducted overall in paper III. A significance level of $p < 0.05$ was chosen, except for the Friedmans ANOVA in paper III. As that significance level can be considered arbitrary (169), exact p -values were reported in the papers and confidence intervals (95%) as appropriate for interpretation. The risk of a type I error has been addressed in paper I and paper II where the majority of inferential statistics were conducted. All statistical analyses were performed in STATA SE (version 14.2; Stata Corp. College Station, TX), except for the Friedmans ANOVA, which was performed in SPSS statistics (version 24.0; IBM Corp. Armonk, NY).

Table 2. Overview of statistical analyses used in papers I–IV

	Study Paper	A I	II	B III	C IV
Descriptive statistics					
Counts		✓	✓	✓	✓
Percentage		✓	✓	✓	
Mean (sd)		✓	✓		
Median (IQR, range)		✓	✓	✓	✓
Confidence intervals		✓	✓	✓	
Non-parametric					
Fisher's exact test				✓	
Friedmans ANOVA (Bonferroni-corrected alpha)				✓	
Mann Whitney U test		✓	✓	✓	
Parametric					
Independent t-test		✓			
Paired t-test			✓		
One-way ANOVA			✓		
Regression (unadjusted and adjusted)					
Ordinal logistic		✓	✓		
Logistic			✓		
Median, bootstrap with a 10,000 replication		✓			
Multinomial logistic		✓			
Hosmer-Lemeshow goodness-of-fit test			✓		
Ordinal Hosmer-Lemeshow goodness-of-fit test		✓	✓		
Multinomial goodness-of-fit test		✓			
ROC analysis		✓			
Effect size					
The Probabilistic Index				✓	

Abbreviations: sd = standard deviation, IQR = Interquartile range, ANOVA = Analysis of Variance, ROC = Receiver Operating Curve

5.4.1 Paper I

Different regression methods were used based on the outcome of interest. For the main outcome—postoperative complications—**ordinal logistic regressions** were conducted due to the ordinal nature of the Clavien-Dindo classification, ranking complication severity from no complication—0 (1) to death—5 (170). The assumption of proportional odds was tested and fulfilled for all models. Proportional odds ensure that the coefficients between each level of outcome groups are the same (171). Even though previous literature examining postoperative morbidity has mainly dichotomized the Clavien-Dindo classification, we chose to handle the data on its appropriate level to avoid misclassification and loss of information. The receiver operating curve (ROC) based on a logistical regression model was used to examine the discrimination ability of each physical test. An area under the curve (AUC) of <0.5 is considered as no apparent accuracy, and 1 is equal to perfect accuracy (172).

For the secondary outcome, LoS in hospital, **median regressions** were conducted as the variable was positively skewed, which is almost always the case with LoS data (173). For the secondary outcome—discharge destination—**multinomial logistic regressions** were performed due to the categorical nature of the variable. When conducting several statistical tests, there is a risk of mass significance. A Bonferroni correction (or similar) could have been applied, dividing the original alpha level chosen with the number of tests conducted, resulting in a lower significance level. This is not recommended if there are more than 5 tests (174). For consistency between the papers of the thesis, we chose instead to report the exact p-values for each test to enable the readers to interpret the values themselves.

5.4.2 Paper II

As the primary aim was to **describe** the short-term changes in physical performance from preoperative (baseline) values to postoperative (discharge) values, mean and standard deviation were reported for each continuous physical performance test and paired t-tests were performed. The secondary aim was to investigate associations for the outcome postoperative mobility, defined as the ability to rise from a chair independently without support. **Logistic regressions** were conducted to assess this. LOWESS curves were conducted to test for the assumption that the relationship between the logits and the outcome was linear (175). The downside of dichotomizing is that we lose statistical robustness. As mobility is a straightforward clinical measure of importance for the patients' independence and might have indirect effects on meso outcomes such as LoS and discharge destination, we chose to dichotomize for clinical relevance in this paper. **Ordinal logistic regressions** were conducted to investigate the association between postoperative physical decline and patient-reported recovery, as the Global recovery scale is an ordinal scale.

5.4.3 Paper III

It has been suggested that a minimum sample size of 24, twelve per group, can be used if the study objective is feasibility and to describe precision of the estimates (176). In our feasibility study we had a sample size of 23 (including two dropouts). Consequently, our feasibility study did not have adequate power to detect the treatment effect of the intervention.

Descriptive statistics were reported for process feasibility outcomes. For scientific feasibility, variations in the treatment effect were reported as median change and 95% confidence intervals (CIs). A Friedman's ANOVA with a Bonferroni-corrected alpha level ($p=0.0167$) were used for repeated within-group analyses, and the Probabilistic Index (based on the Mann-Whitney statistics) was used to calculate effect size between groups (177). Random error in a study is dependent on sample size, and increases with smaller sample sizes. Reporting CIs can help estimate the random errors and provide information regarding the precision of the estimate (123, 129).

5.4.4 Qualitative analysis (paper IV)

The qualitative analysis was performed using Elo & Kyngäs' (132) inductive approach and incorporated the following phases:

- Preparation state—Emelie Karlsson (EK) transcribed all interviews and read them again before starting to identify units of meaning, related to the study objective, from each interview. Meanwhile Mia Bergenmar (MB) and Malin Nygren-Bonnier (MNB) read the transcripts.
- Organization—EK conducted open coding of the identified text units on the transcripts, and grouped the codes in a Microsoft Excel coding sheet. We followed the recommendation from Elo et al. 2014 (178) that “one researcher is responsible for the analysis and others carefully follow up on the whole analysis process and categorization.” MB and MNB verified the codes and groupings, and in joint discussions and revisions the codes were grouped into possible sub-categories (EK, MB, MNB). In the final group discussion, categories were abstracted and staged in two main categories. The iterative process in the analyses was conducted to enable sufficient abstraction during categorization, and minimize the risk of excessive and overlapping categories.
- Reporting—To ensure conformability, we chose to stay as close to the text material as possible initially, and incorporated more interpretation from the researchers in the final stage of the results ending up with a theme (178).

5.5 ETHICS

The research included in the thesis is conducted according to the ethical principles of the Declaration of Helsinki (179). The overall research project is approved by the regional ethical committee in Stockholm (Dnr: 2015/1179-31). Additional applications were made during the research process due to modification of the exercise intensity in the intervention of study B (Dnr: 2016/1587-32), additional timepoints for follow-up in study A (Dnr: 2016/2162-32),

the interview study to highlight the perspectives of the patients, as well as revised written patient information and additional sites for recruitment for study C (Dnr: 2017/1246-32). The group in focus for participation can be considered a vulnerable group due to reduced general health, recent information regarding a possibly malignant tumor and facing major surgery. It was clearly stated to eligible patients in writing and orally that participation was optional, and that they could withdraw at any time during the process without affecting their care. Patients brought their written informed consent (signed in their home or at the surgical office) to the first assessment and prior to randomization. The assessments of physical performance were coordinated to regular hospital visits as often as possible to minimize travel for the participants. The collected data was coded throughout the process, handled according to the Public Access to Information and Secrecy Act and stored in a safe only accessible to those responsible for the research, to ensure confidentiality (180). The processing of personal data was handled according to the Data Protection Act until the 25th of May 2018, and thereafter according to the General Data Protection Regulation (GDPR).

In study A, the participants were provided with more frequent checkups by a health care professional regarding their physical status, which can be considered a benefit. The overall data in general and self-reported data in particular were reviewed and compared for the participants (n=5) scoring <24 points on MMSE regarding the cognitive status. No major deviation in performance or answers from these participants, compared to the rest of the study population, were noted. The main ethical consideration in study B was the delay of surgery by 1 week in the intervention group. However, only participants where no medical risk regarding cancer outcome existed with a short delay of surgery were approached. The intervention may have led to soreness from the physical exercise; still, the health risk of physical inactivity is considered to be greater. The exercise was monitored by the physical therapist at each supervised session and modified if needed. In addition, it may be questioned that the control group only received general physical activity recommendations even though it is evident that physical exercise has a positive effect overall. Nevertheless, in Sweden preoperative exercise is not yet a part of standard care, and current literature on the topic involves interventions of 4 weeks or longer, whereas we do not know if we can gain any physical effect in only 2–3 weeks of exercise and if the program is feasible. In study C, the informants might have felt a social desirability to answer some of the questions a certain way in front of the interviewer. Nevertheless, this is not thought have led to any discomfort and the interview was an opportunity for the informants to express their own views on physical exercise as a possible way to optimize physical performance prior to surgery.

If positive results of the overall project can be shown, the knowledge can benefit older adults in general undergoing abdominal surgery. Conversely, if no effect can be shown, the pros of being physically active in general are considered to outweigh the cons that might appear, such as muscle soreness. The age group (≥ 70 years of age) in the studies is an underrepresented group in clinical research but nevertheless a group frequently appearing in health care and with great heterogeneity, and research in this age group is of utmost importance to understand the epidemiology in this field and tailor interventions to improve outcomes.

6 RESULTS

This section summarizes the main findings of the studies in the thesis, divided into study A (papers I and II) and study B/C (papers III and IV). Detailed results can be found in each publication or manuscript.

Together, 237 patients over the age of 70 were included in the three studies. Eight participants were excluded after inclusion due to medical or logistical issues (figure 8). Table 3 contains an overview of participant characteristics. For comparability between the studies, the table also includes the mean and standard deviations for papers III and IV (other central and variability measures are reported in the publications). The variations (standard deviations), regarding demographics and clinical data of the study population, are greater in paper III and manuscript IV compared to papers I and II due to smaller sample sizes. Possible reasons for differences in the characteristics of the study populations are the localization of recruiting sites as well as different cancer types included in papers I and II (gastrointestinal cancer) compared to papers III and IV (colorectal cancer).

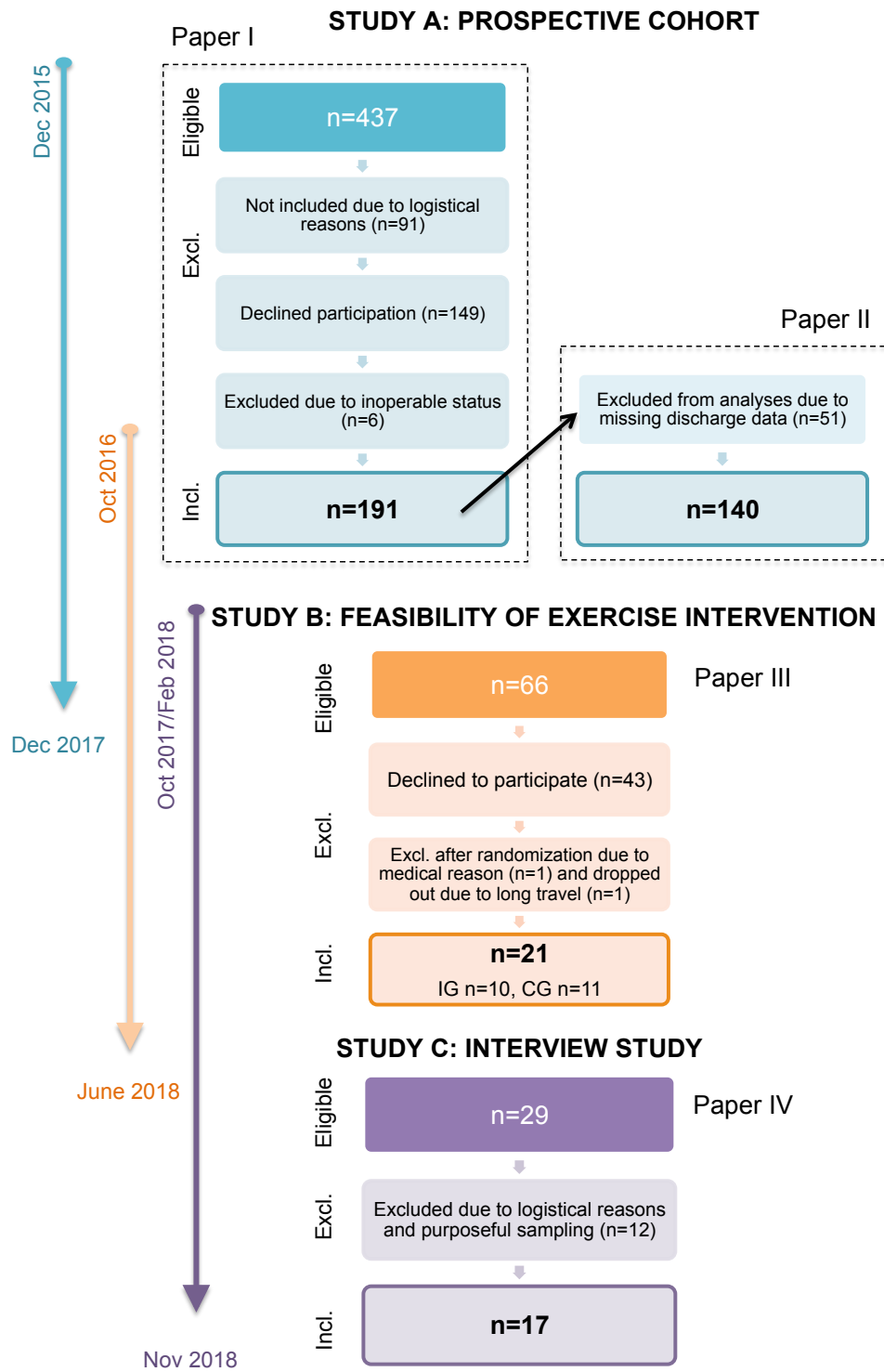


Figure 8. Synthesized flow chart of recruitment and inclusion in the studies in the thesis. Arrows next to the figure illustrate the time period of each study. Abbreviations: IG=Intervention group, CG=Control group (i.e. standard care group)

Table 3. Overview of demographic and clinical data of study participants per paper

	Paper I	Paper II	Paper III		Paper IV
	n=191	n=140 ^a	IG n=10	CG n=11	n=17
Age, mean (sd)	76.0 (4.4)	76.0 (4.6)	81.4 (6.0)	75.0 (5.0)	75.1 (5.3)
Male sex, n (%)	115 (60.2)	88 (62.9)	4 (40.0)	4 (36.0)	9 (52.9)
Living situation, n (%)					
<i>With partner</i>	137 (71.7)	104 (74.3)	5 (50.0)	5 (46.0)	11 (64.7)
<i>Alone</i>	54 (28.3)	36 (25.7)	5 (50.0)	6 (54.0)	6 (35.3)
Education, n (%)					
<i>Compulsory level</i>	27 (14.2)	20 (14.3)	1 (10.0)	2 (18.2)	4 (23.5)
<i>Above compulsory—below uni</i>	77 (40.3)	59 (42.1)	5 (50.0)	6 (54.5)	5 (29.4)
<i>University</i>	69 (36.1)	48 (34.3)	3 (30.0)	3 (27.3)	8 (47.1)
<i>Other</i>	18 (9.4)	13 (9.3)	1 (10.0)	—	—
Cancer type, n (%)					
<i>Colon</i>	60 (31.4)	49 (35.0)	9 (90.0)	9 (82.0)	10 (58.8)
<i>Rectal</i>	25 (13.1)	23 (16.4)	1 (10.0)	2 (18.0)	7 (41.2)
<i>Liver/liver metastases/biliary</i>	47 (24.6)	27 (19.3)	—	—	—
<i>Pancreas</i>	59 (30.9)	41 (29.3)	—	—	—
Charlson Comorbidity Index ^b , median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	1 (0-3)	2 (1-4)
Surgical approach, n (%)					
<i>Open</i>	144 (75.4)	104 (74.3)	3 (30.0)	3 (27.0)	9 (52.9)
<i>Laparoscopic</i>	47 (24.6)	36 (25.7)	7 (70.0)	8 (73.0)	8 (47.1)
Tumor stage, n (%)					
<i>0</i>	28 (14.7)	20 (14.2)	—	2 (18.2)	—
<i>I</i>	34 (17.8)	25 (17.9)	—	3 (27.3)	4 (23.5)
<i>II</i>	31 (16.2)	25 (17.9)	5 (50.0)	1 (9.1)	5 (29.4)
<i>III</i>	59 (30.9)	47 (33.6)	4 (40.0)	5 (45.4)	5 (29.4)
<i>IV</i>	39 (20.4)	23 (16.4)	1 (10.0)	—	3 (17.7)
Neoadjuvant treatment, n (%)					
<i>Radiation therapy</i>	18 (9.4)	15 (10.7)	1	2	2
<i>Chemotherapy</i>	18 (9.4)	11 (7.9)	—	—	1
<i>Both</i>	9 (4.7)	8 (5.7)	—	—	—
Laboratory markers, mean (sd)					
<i>Hb, g/L</i>	127.1 (16.3)	127.0 (16.8)	119.7 (15.7)	123.5 (12.8)	—
<i>CRP, mg/L</i>	10.2 (16.9)	10.5 (17.4)	14.4 (33.3)	5.7 (5.2)	—
<i>Albumin, g/L</i>	34.5 (4.2)	34.5 (4.3)	36.1 (2.5)	34.5 (3.4)	—
MNA-SF, median (IQR)	11 (9-12)	11 (9-12)	—	—	—
Global health status, mean (sd)	66.1 (22.1)	67.1 (21.6)	57.5 (25.6)	65.2 (14.8)	—
Self-reported physical activity, PASE, mean (sd)	102.3 (56.2)	105.8 (58.7)	79.6 (55.0)	84.8 (35.0)	96.2 (48.2)

Abbreviations: IG=Intervention group, CG=Control group (i.e. standard care group), IQR=interquartile range, hb=hemoglobin, CRP=C-reactive protein, MNA-SF=Mini Nutritional Assessment Short-Form, PASE= Physical Activity for the Elderly scale. ^a 140 of the participants also presented in paper I, ^b Not age-adjusted.

6.1 STUDY A (PAPERS I AND II)

The prospective cohort study, encompassing papers I and II of the thesis, provided us with findings from the micro to meso levels (figure 9). Micro (patient) level outcomes were postoperative complications, postoperative mobility and self-reported recovery. Meso (organizational) level outcomes were length of stay in hospital and discharge destination. In the long run this may also affect the macro (policy) level for recommendations, guidelines and implementation.

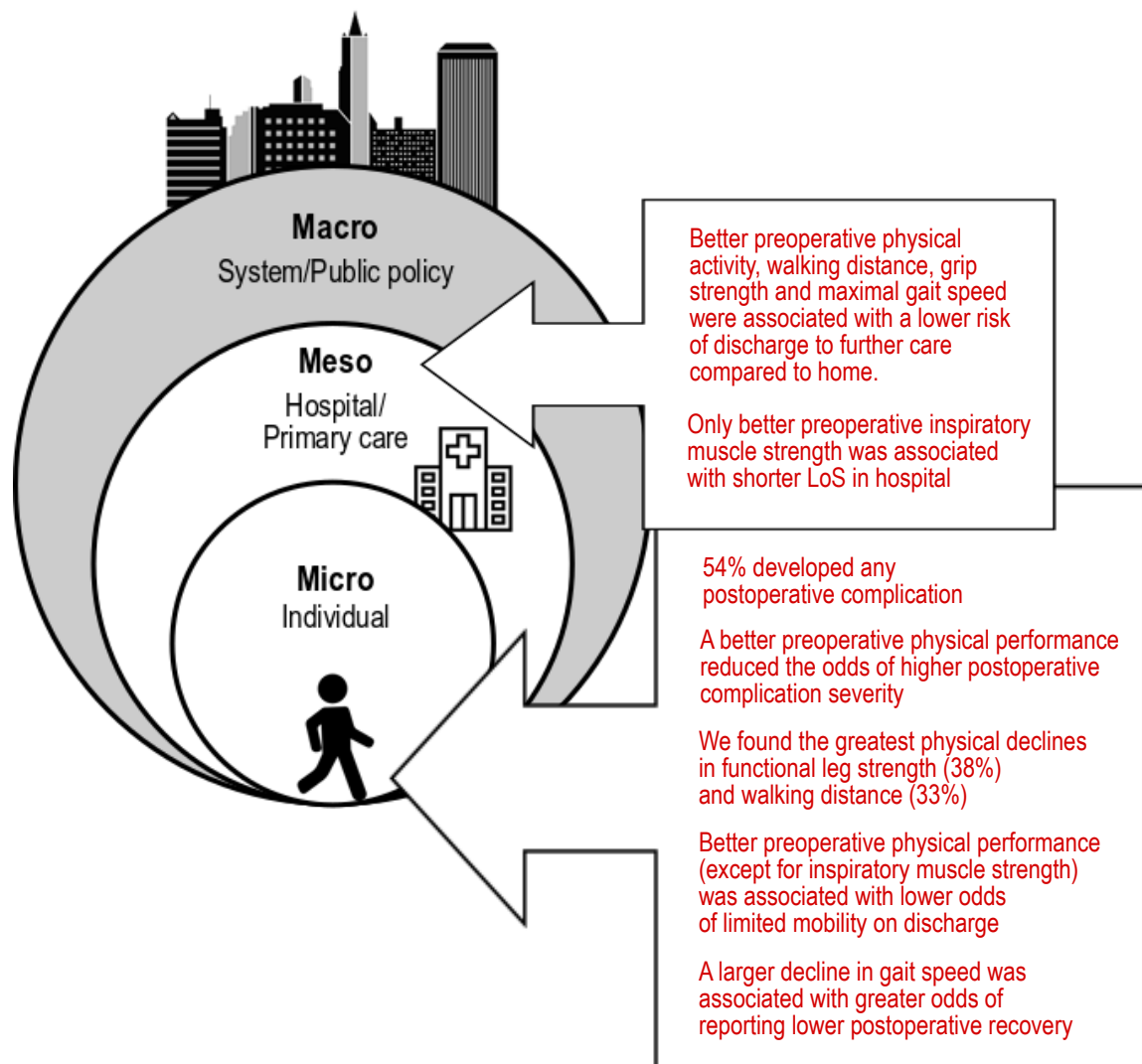


Figure 9. Summary of findings on micro and macro levels in study A (paper I and II)

On the **micro level**, a minimum of one postoperative complication was seen in 54% (n=104) of the study population (figure 10). Thus the study population in question had a high rate of complications, which might indicate that it includes high-risk patients even though we had a high declining rate at recruitment. Nineteen (18%) of the complications were infectious, such as pneumonia and sepsis; 21 (20%) were cardiovascular such as tachyarrhythmia, heart failure, and myocardial infarction; 2 (2%) were neurological, such as transient confusion and ischemic stroke; 39 (38%) were surgical, such as wound dehiscence, anastomotic leakage, and intra-abdominal abscess; and 23 (22%) were other complications such as total parenteral nutrition (as seen in fig. 2 of paper I). As 31 (30%) of the 104 individuals who developed postoperative complications experienced more than one complication, a calculation of the Comprehensive Complication Index (CCI) added extra value regarding the cumulative burden of complications in each participant (median 8.7, IQR 0-26.2, paper I page 1764).

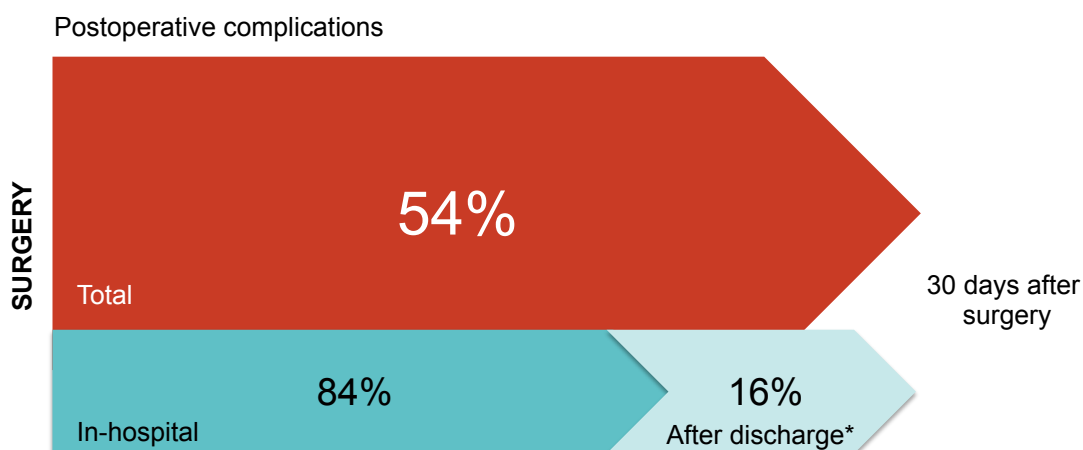


Figure 10. Frequency of postoperative complications in the study population from surgery until 30 days postoperatively, divided into in-hospital complications and complications occurring after discharge *to home or other care facility

When adjusting for possible confounders, a better preoperative physical performance including functional physical capacity (6 MWT), functional leg strength (30 s Chair Stands Test), grip strength, inspiratory muscle strength (MIP), and gait speed (habitual and maximal 10 m walking test) had a protective effect on postoperative complication severity (figure 11). When interpreting the magnitude of the estimate of interest in each model, it must be taken into account that the different physical performance tests are reported in their appropriate unit and not in standardized units for all models.

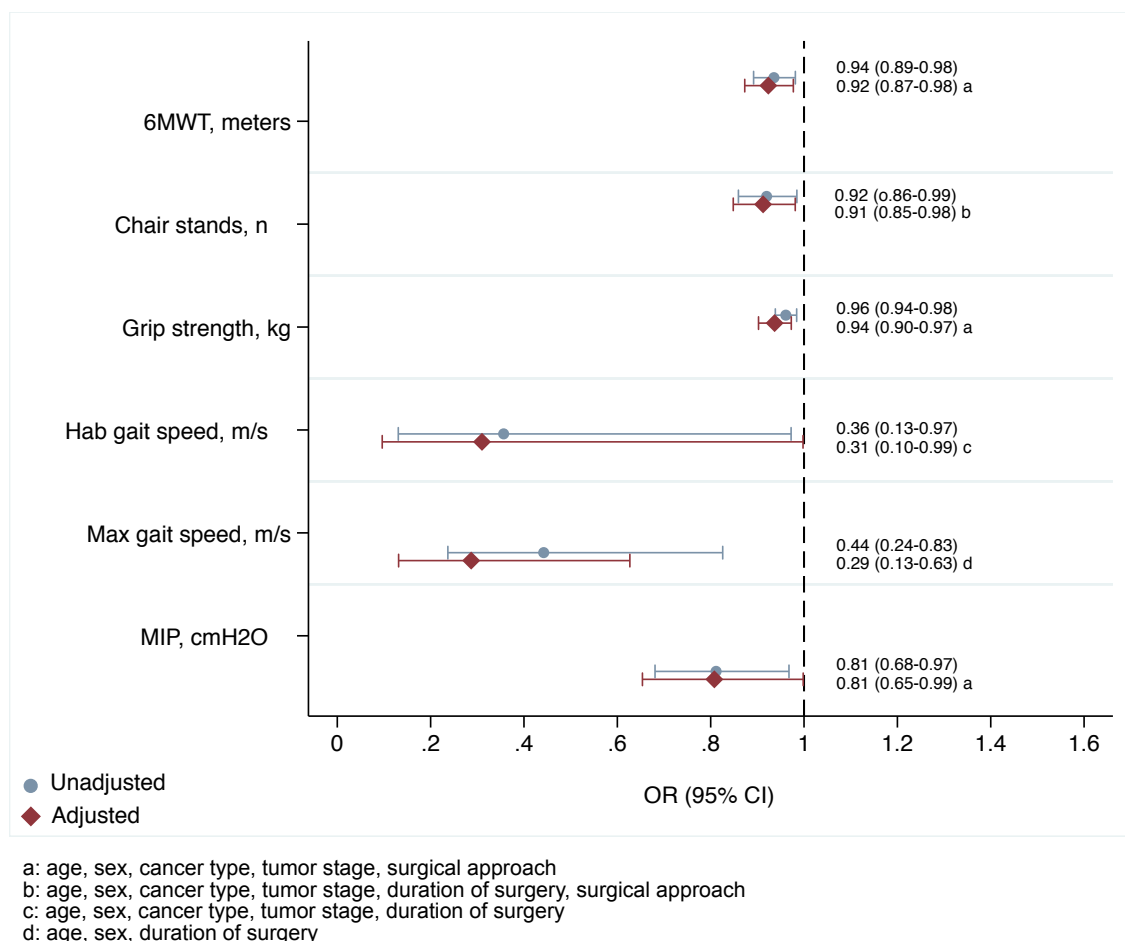
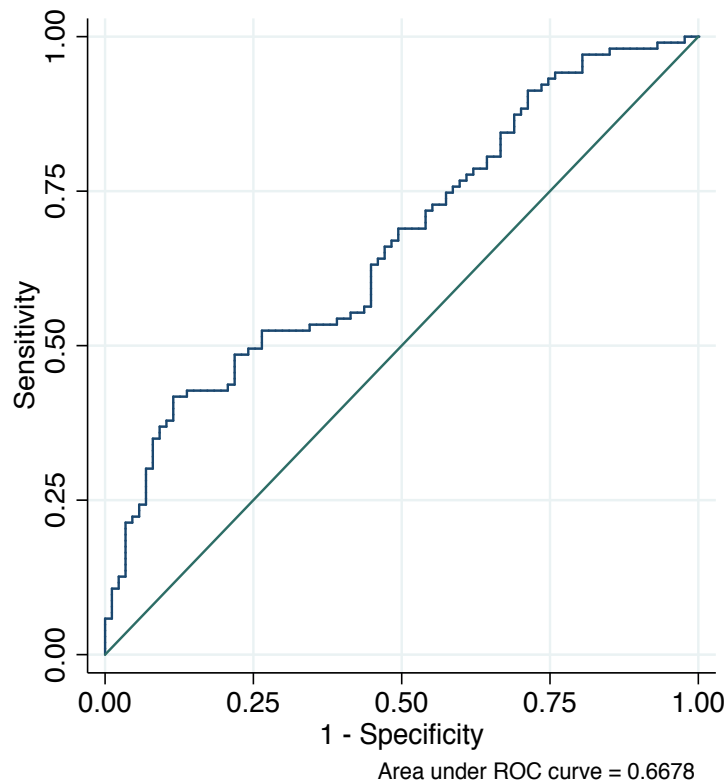
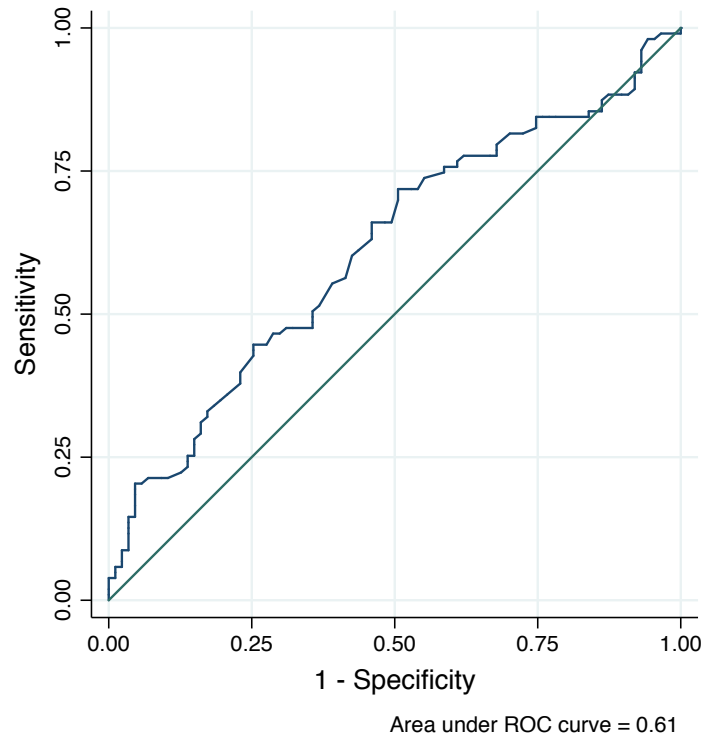


Figure 11. Multivariable ordinal regression models for each explanatory physical performance variable (Y axis) and the outcome variable postoperative complication severity, reported as odds ratios (OR) and 95% confidence intervals (95% CI). Abbreviations: 6MWT= Six-Minute Walk Test, MIP=Maximal Inspiratory Pressure.

The model with maximal gait speed (with a cut off of 2.03 m/s) had the univariate “best” AUC (0.61, sensitivity 0.74, specificity 0.45) of the performance tests when doing ROC curves based on our study sample (figures 12 a). In addition, this is a clinically relevant and easy to administer test for the clinical setting. In subgroup analyses the AUC for males was 0.59 and for females 0.64. When interpreting the AUC, one should be aware that a single test hardly explains the whole picture; thus a model including several variables would result in a higher AUC (0.67), as seen in the second ROC curve in figure 12 b.



Figures 12 a–b. Receiver Operating Curve (ROC) of maximal gait speeds
discrimination ability of complication incidence (a), and for the adjusted regression model including maximal gait speed in figure 11 (b). Sensitivity=the amount of individuals rightfully classified as having the outcome, and 1-Specificity=1—the amount of individuals rightfully classified as not having the outcome.

Eighty-four percent of the postoperative complications registered within 30 days after surgery in the study population occurred in-hospital (i.e. before discharge to other destinations), and 16% occurred after discharge, often resulting in readmission to the hospital (figure 10). Consequently, health and recovery during the in-hospital period is of utmost importance as most complications occur early on after surgery.

We saw a 6–38% reduction in the different physical performance tests from preoperative to postoperative values, also in the part of the population who did not experience any postoperative complications (n=67). This is similar to the decline in the total study population as reported in table 2 of paper II (9–38%), and gives us a sense of “the solely surgical effect” on physical performance. This decline was higher when undergoing open surgery compared to laparoscopic, and if having pancreatic surgery (as seen in figure 2 in paper II). The greatest declines between pre- and postoperative physical performance in the total study population appeared in functional leg strength (on average 5 chair rises, corresponding to a 38% decline) and walking distance (on average 157 m, corresponding to a 33% decline). It has been suggested that being able to mobilize postoperatively is one of the discharge components that takes the longest for patients to achieve (58). In our data, not being able to rise from a chair independently on discharge increased the risk of being discharged to a geriatric unit or care facility compared to home (Relative Risk Ratio (RRR)=9.29; 95% CI 2.0–43.0; p=0.004).

Better preoperative physical performance, except for inspiratory muscle strength, was associated with lower odds of limited mobility on discharge (as seen in table 3 in paper II), Respiratory muscle strength not being associated with postoperative mobility was somewhat expected, given that the outcome mainly incorporates peripheral muscle strength and not respiratory muscle strength. A greater decline in gait speed was significantly associated with greater odds of reporting lower postoperative recovery in multivariable analysis (OR=1.03; 95% CI 1.01–1.06; p=0.014–0.015). Functional leg strength lost significance when controlling for confounders.

On the **meso level**, LoS in hospital and discharge destination were addressed, as these are outcomes with health economical implications for the health care system. This knowledge may help guide health care discharge planning and the further care pathway for each individual at an early stage.

Better preoperative inspiratory muscle strength alone was associated with shorter LoS in hospital (coefficient= -0.416; 95% CI -0.825/-0.009; p=0.045). In addition, preoperative MIP was significantly associated with postoperative pulmonary complications (adjusted for age, sex, and pulmonary disease) as reported in paper I (OR=0.44; 95% CI 0.27–0.74; p=0.002). Better preoperative physical activity level, walking distance, grip strength, and maximal walking speed reduced the odds of being postoperatively discharged to further care rather than to home, but not to a rehabilitation unit (seen in table 4 in paper I). In Sweden, discharge to a rehabilitation facility corresponds to active rehabilitation and might primarily involve fit older adults. Our results indicating no difference in physical performance between those discharged to home or rehabilitation in paper I, are therefore, expected in the national context.

6.2 STUDIES B AND C (PAPERS III AND IV)

Study B showed that a preoperative supervised home-based physical exercise intervention seems feasible in respect to compliance (97%) and acceptability, and can be conducted for older adults with similar physical status as the study population prior to colorectal cancer surgery. Nevertheless, the intervention was not feasible with respect to recruitment (23 people were included out of 66 approached for participation during an 18-month period), resulting in a low recruitment rate and possible recruitment bias. The most common reasons for declining were time-related, as seen on page 6 in paper III. Consequently, modifications were suggested for a larger scale trial to improve recruitment (see modification points on page 16 in paper III), as well as a need for a deeper understanding regarding the patients' attitudes towards and perception of preoperative physical exercise investigated in study C.

In study C, a gap appeared between awareness of the benefits of being physically active to prepare for surgery, and to actually taking action to undertake physical activity and exercise (figure 13). The reasons contributing to the gap in this context were multifactorial (previous experiences, current environment and care context, as well as intrinsic components). Both barriers to and motivators for being physically active in the preoperative context were described (pages 11, and 13–14 in manuscript IV), and active support from others emerged as an opportunity to overcome the gap.

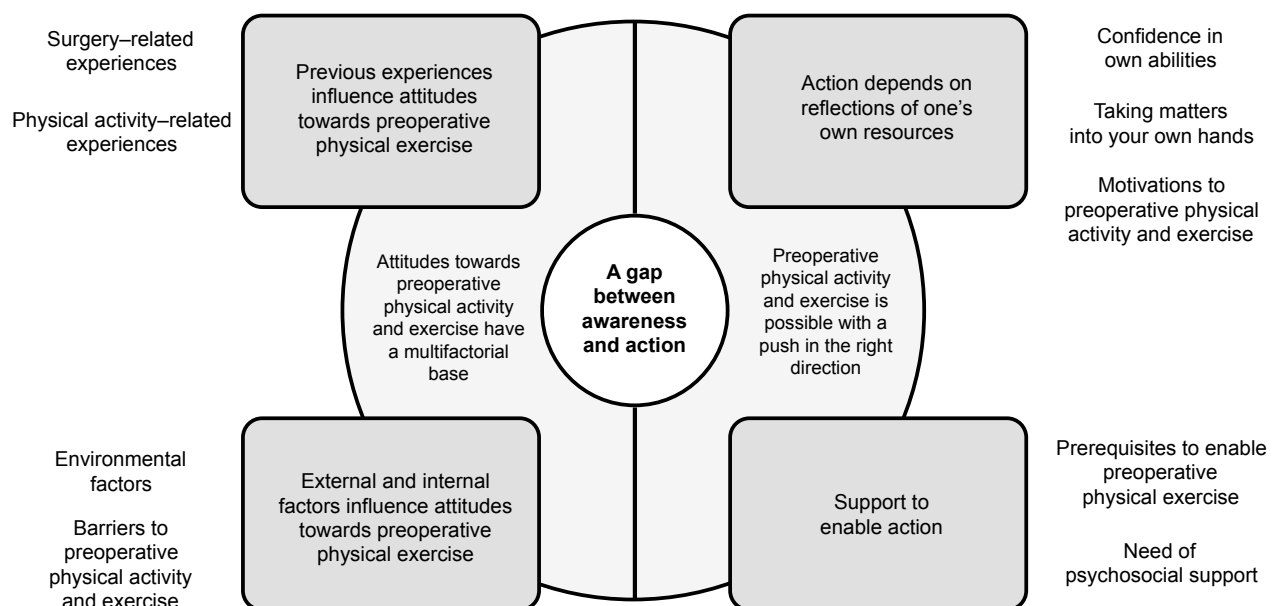


Figure 13. Overview of findings in study C from sub-categories in the periphery to the theme in the center of the figure.

When synthesizing free-text answers from participants in the exercise intervention in study B with descriptions from the informants in study C, we found that support and guidance from health care professionals to enable physical exercise, the social interaction and active support during exercise, and the importance of making the waiting time meaningful are emphasized in both studies (figure 14). The time-related reasons (time-consuming examinations, no time for intervention, and feeling stressed) for declining reported in paper III were also described in the category “External and internal factors influence attitudes towards preoperative physical exercise” as competing focus and other priorities in manuscript IV.

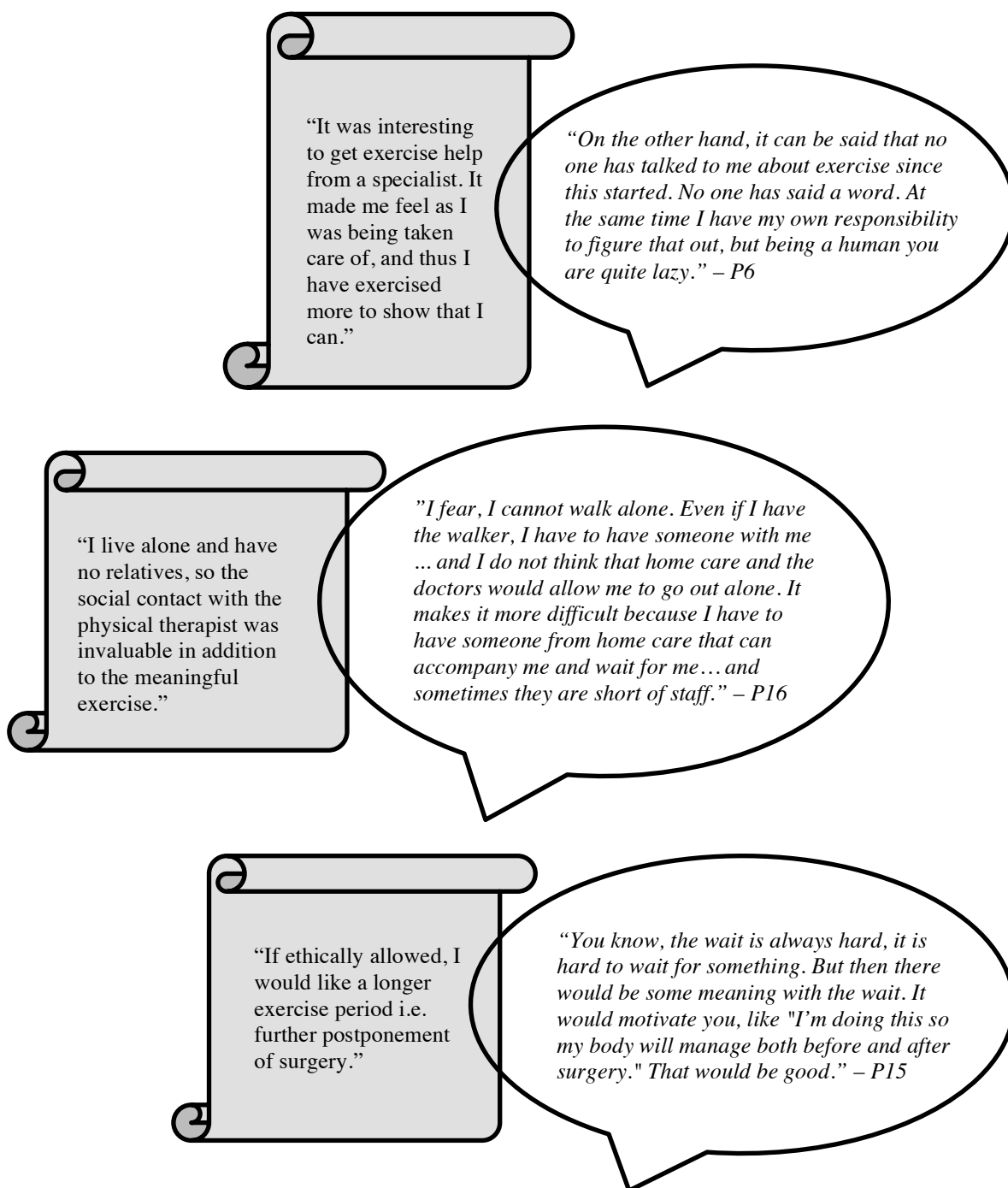


Figure 14. Links between free text answers in grey (table 2, paper III) from the participants of the exercise intervention in study B and interviews in study C.

Despite a small sample size and thus no intention to calculate effects of the exercise program in study B, a significant improvement of inspiratory muscle strength arose as a secondary finding of scientific feasibility within repeated measures in the intervention group (+17 cmH₂O; p=0.01), and in comparison with the standard care group (-2 cmH₂O; effect size 0.90). Possible reasons for this might be that the median goal intensity (figure 15) was partly reached and a higher progression was achieved for the inspiratory muscle training (figure 16), compared to the functional strength and aerobic endurance training.

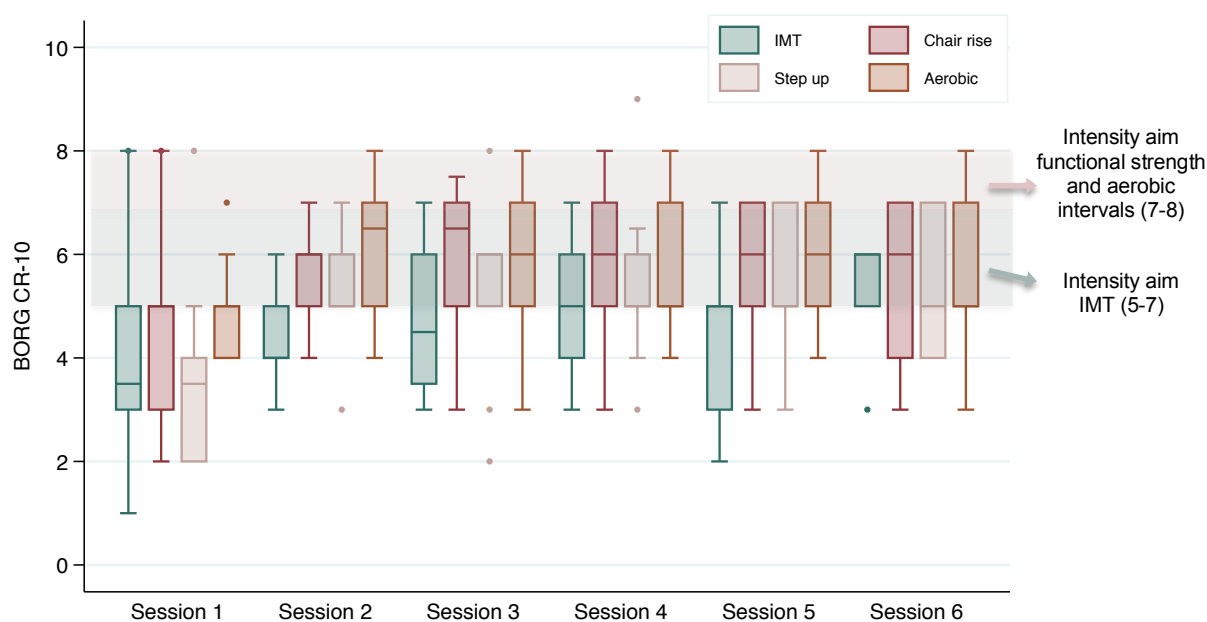


Figure 15. Median perceived exertion on the Borg CR-10 scale per exercise modality for each supervised session in the intervention group (n=10). Abbreviations: IMT=Inspiratory muscle training

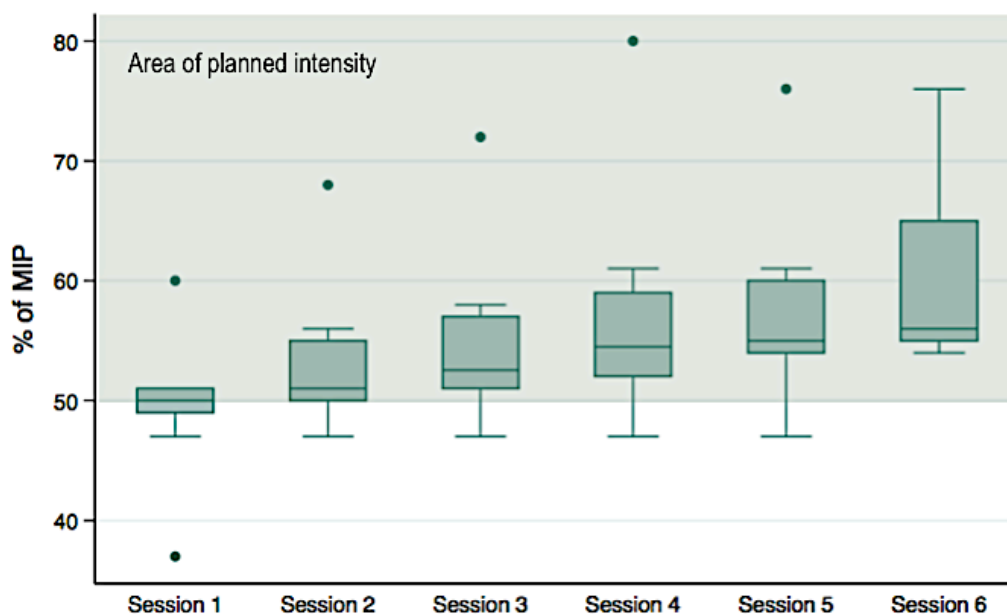


Figure 16. Progression of inspiratory muscle training load in the intervention group (n=10) over supervised exercise sessions. Abbreviations: MIP=Maximal inspiratory pressure.

Half of the participants in the intervention group, compared to 18% in the standard care group, improved more than the smallest meaningful change of 20 meters in walking distance (181). The corresponding numbers in regard to a 16 cmH₂O improvement in MIP (147) were 60% in the intervention group compared to 9% in the standard care group. The median duration of the exercise intervention was 17 days (range 14–24).

In paper II of study A, the colorectal cancer group declined on average 122 m (27%) in 6 MWT, 4 chair rises in CST (33%), 0.22 m/s (17%) in habitual gait speed and 0.44 m/s (24%) in maximal gait speed, and 15 cmH₂O (20%) in MIP between pre- and postoperative measures, solely by undergoing surgery. The intervention group in study B declined on average less in physical performance in all tests compared to the colorectal cancer (CRC) group in paper II, as the standard care group declined more or somewhat equally to the CRC group in paper II in four of five tests (table 4).

Table 4. Average change in physical performance from baseline to postoperatively in the intervention group (IG) and standard care group (CG) of study B, and in comparison to the CRC group in study A.

Variable		Value, mean (sd)				
		Preoperative	Postoperative	Change	Decline	Decline compared to CRC group in study A
6MWT, meters	IG	415 (140)	342 (127)	-73	18%	↓
	CG	436 (105)	258 (135)	-178	41%	↑
30 s CST, n	IG	10 (5)	9 (5)	-1	10%	↓
	CG	12 (4)	10 (5)	-2	17%	↓
Gait speed, m/s <i>Habitual</i>	IG	1.04 (0.28)	0.97 (0.28)	-0.07	7%	↓
	CG	1.03 (0.25)	0.82 (0.24)	-0.21	20%	↑
<i>Maximal</i>	IG	1.60 (0.45)	1.26 (0.36)	-0.34	21%	↓
	CG	1.48 (0.34)	1.15 (0.33)	-0.34	23%	↘
Inspiratory muscle strength, cmH ₂ O	IG	68 (36)	78 (32)	+10	0% (+15)	↓
	CG	63 (25)	51 (26)	-11	17%	↘

Abbreviations: CRC=Colorectal cancer, IG=Intervention group, CG=Standard care group, 6MWT=Six-Minute Walk Test, CST=Chair Stand Test. ↓=less relative decline than CRC group in paper II, ↑= more relative decline than CRC group in paper II, ↘=similar relative decline as the CRC group in paper II

7 DISCUSSION

7.1 SUMMARY AND DISCUSSION OF MAIN FINDINGS

- Better preoperative physical performance reduces the odds of adverse postoperative outcomes (complication severity, length of hospital stay, discharge destination, and postoperative mobility) in older adults undergoing abdominal cancer surgery. Thus, preoperative physical performance is associated with postoperative outcomes on both the micro and meso levels. For example, preoperative physical performance is associated with postoperative mobility on the micro level, which can in turn affect LoS and discharge destination, thus the meso level. In addition, screening of physical performance (in combination with conventional preoperative risk assessments) can provide additional information for decision making regarding each patient's surgical pathway and, hopefully, facilitate shared decision-making with the patient.
- A short-term, supervised, home-based exercise program at a high level of exertion is feasible with respect to compliance and acceptability in older adults prior to colorectal cancer surgery. However, recruitment was low and needs to be further improved to reach the patients who need it the most, and to reduce the risk of recruitment bias.
- Incorporated, the older patient's thoughts regarding preoperative physical exercise, including the multiple influencing factors and the support needed to enable action, should be taken into consideration during the preoperative period. This could potentially bridge the gap between awareness of the benefits of being physically active and actually being physically active.

7.1.1 Preoperative risk stratification and postoperative outcomes (Papers I and II)

The incidence of postoperative complications found in study A is higher than the national data, but somewhat comparable to previous studies including similar populations agewise (182, 183). Cardiopulmonary complications are most common and the deadliest. In our study population, the surgical complications were more common, but often at a lower complication severity than the cardiopulmonary complications. After surgical complications, cardiovascular and infectious complications appeared frequently. It is more straightforward that we might be able to affect the cardiovascular complications by physical exercise in older adults as it reduces inflammatory markers, improves cardiac output, improves gas exchange and vascularization, and insulin sensitivity (72), compared to the surgical complications. Nevertheless, if the patient's overall physical health is optimized, they might be able to withstand the surgical complications better and wound healing might be affected by improved circulation (184). The consequences of postoperative complications will affect both the patient (micro level) through reduced recovery (39), and health care (meso level) through increased hospital costs (185).

Regarding the association between preoperative physical performance and postoperative outcomes, the central part of the interpretation is that several of the physical tests proved to be independently associated with the outcomes. If we had standardized the units of the estimates, they would have been comparable between models. However, that would lower the clinical interpretation of each model. Maximal gait speed seems to be more important than habitual in our material; one reason might be that maximal gait speed indicates a person's functional capacity for coping in daily life (143). Gait speed has been shown to be associated with mortality and/or morbidity after cardiac surgery and gastrectomy (186, 187). In addition, a gait speed below 0.8 m/s is incorporated in sarcopenia criteria and a gait speed over 1.2 m/s is needed to cross a street safely (143, 188). Both gait speed and chair rise are considered to be important functional assessments in everyday life in the older population, as well as predictors for negative health outcomes such as limited mobility and death (138, 189).

The ROC curve only revealed moderate discriminative ability of gait speed on postoperative complications, and it must be kept in mind that the cut-off value is based on study A's population. A full analysis with, for example, cross validation or comparison with an independent dataset is needed to investigate the predictive value of gait speed (190). In addition, there will always be an issue of residual confounding. Notably, I do not suggest that preoperative decision-making be based solely on a brief test of physical performance such as gait speed or walking distance. It should be combined with conventional preoperative screening. Furthermore, the added information that physical assessments can provide is valuable to incorporate in multidisciplinary meetings regarding the patients conducted by health care professionals prior to surgery. This is because it has been shown that the discussions regarding older patients' physical status in multidisciplinary meetings can be somewhat general and non-specific (191).

As the majority of complications appear in-hospital, shown in our cohort study and indicated in previous research (192), this time period requires extra attention. Knowing how physical performance changes from preoperative baseline values to postoperative values (as described in paper II) could be useful in addressing the effects outside of the normal variations in decline for future intervention studies including older adults undergoing abdominal cancer surgery. The magnitude (9–38%) of physical decline found in paper II of this thesis, is somewhat consistent with earlier findings (55, 56) of a reduction corresponding to 5–50% and 5–34% in muscle function and functional capacity after surgery. The reason for a higher upper boundary in the earliest finding might be that surgical techniques have improved and postoperative care has changed through such measures as the implementation of Enhanced Recovery After Surgery (ERAS/ERP) programs. At the hospital sites where our data was collected, ERAS/ERP are already implemented as standard care for colorectal and liver resections. In the study sample of study A, 55% of the participants were planned for the ERAS/ERP pathway prior to surgery. However, due to insufficient registration of compliance to the mobilization module of the programs in the medical records, which is a limitation of our data, it was difficult to control for. After abdominal surgery, an individual may lose as much as 0.5 kg of lean body mass per day due to the protein catabolism caused by the

surgical stress (27). Consequently, functional leg strength being the most affected might not be a surprise as the CST movement involves the activation of large muscle groups as well as an explosive component with repeated movements over a short period of time.

We had hypothesized that comorbidity would be an important factor in the association analyses of papers I and II. This was not the case in our study population. One explanation might be that the Charlson Comorbidity Index does not take the disease severity or interaction between diseases into account. Recently, it was suggested that Charlson might not be sensitive enough to detect the risk of postoperative adverse outcomes in an older cancer population (17). Furthermore, it was implied that the effect of disability on mortality is superior to the effect of multimorbidity in older adults (193, 194).

Regarding the association between postoperative decline and patient-reported postoperative recovery, the findings indicate that the patient-reported recovery component is much more complex than just being associated with physical aspects. This is also demonstrated in the PRP scale, which consists of five different domains (physical symptoms, physical function, psychological, social, and activity). Other influential factors might be patient expectations, baseline physical status, and mental status. Previous literature has indicated that patients who had better health preoperatively were more prone to report good recovery regarding physical symptoms 1 month after surgery (64). Regarding the physical domain of self-reported recovery, one could combine physical measures and wireless monitoring with the self-reports to add extra and comparative information (195).

On the meso level, only better preoperative inspiratory muscle strength was associated with shorter LoS in the hospital. One possible reason for this is a mediating effect of postoperative pulmonary complications (PPCs) on the association between MIP and LoS. Thus, there was a significant association between MIP and PPCs on the micro level (adjusted for age, sex, and pulmonary disease) as reported in paper I (OR=0.44; 95% CI 0.27–0.74; $p=0.002$, page 1764). The significant associations between self-reported physical activity and median LoS attenuated in multivariable analysis in our data, in contrast with some previous findings (196) but are consistent with others (197). This is mainly considered to be an issue of a small sample size as seen by a wider CI but no substantial change of the estimate. Another possible reason could be the different physical activity questionnaires used in studies. Higher PASE scores in our studies were mainly collected using domestic charts, which can be considered of lower intensity than planned physical exercise. However, lower intensity activities are the most common form of physical activity performed by older adults (73).

Better preoperative physical performance (self-reported physical activity level, walking distance, grip strength, and maximal gait speed) significantly reduced the risk of being discharged to further care rather than to home in our study sample. In study A, 41% were discharged to home, 50% to a rehabilitation unit, and 9% to geriatric or further care. Previous research has reported numbers such as 10% discharged to further care, defined as “skilled nursing homes or rehabilitation,” after abdominal surgery (51), and 27% defined as “home health or non-home destination at discharge” after colorectal cancer surgery (198).

Differences in health care systems between countries can explain the discrepancy in the findings, as well as the definition of further care. In our study, further care excluded rehabilitation units, which were included in the other studies. In addition, few observations (n=20) in our further care category may be the reason the estimate loses significance for e.g. habitual gait speed and functional leg strength from unadjusted to adjusted models.

7.1.2 Aspects on preoperative physical exercise (Papers III and IV)

Low recruitment and compliance to exercise regimens have been addressed as an issue earlier in the field of prehabilitation (99, 100, 107). Low recruitment might lead to selection bias, in turn reducing the external validity of findings. Reasons for low recruitment in our and other studies in the research field might be the context of complicated recruitment pathways (as we incorporated the intervention into routine clinical practice) in a short and stressful time period. Furthermore, an active intervention for the patient means that they need to take part in the intervention and not just passively receive treatment. As prehabilitation is an emerging area of interest in health care, preoperative exercise is not yet well known for the patients, as shown in paper IV; thus it is probably a challenge to engage in something that is unknown. The “QuinteT Recruitment Intervention (QRI)” by Donovan et al. (199) includes a structure to reduce recruitment difficulties, which suggests that we first need to address the challenges by understanding the reasons for the difficulties. The qualitative study (paper IV) in this dissertation was undertaken for this very reason. Eligibility and recruitment logs were also conducted, and participants who declined were asked (optionally) to give their reason for not wanting to participate. Some studies have demonstrated that study participants are more active overall compared to patients who decline participation (200, 201). In contrast, others have implied that study participants report poorer health and lower activity (202, 203).

As the most common reasons for declining in study B were time-related, and descriptions of competing focus and priorities during the preoperative period appeared in the category “External and internal factors influence attitudes towards preoperative physical exercise” in study C, one additional modification to add in a larger trial is to map the clinical cancer pathway and intervene earlier in the preoperative pathway. This would generate more time for optimization and for the patient to adapt to a behavior change. Nevertheless, it would also mean that we have to approach the patient during an emotional time after receiving a cancer diagnosis. Thus, we need to address the responsiveness and adaptability of the participants, as there might be a startup journey in the beginning and a challenge to reach behavior change.

The preoperative time frame is based on the shortest time that can be achieved when taking the medical conditions and health care organization into consideration. Nevertheless, no time is set aside for the individual person’s potential need for reflection regarding the treatment and care process after receiving the diagnosis, which might be important to consider (204). Seven out of nine participants in the intervention in study B would have preferred a longer intervention period. This is particularly important to keep in mind when it comes to older adults with multi-morbidity and sometimes a lack of a social network. When looking at the free text answers from study B, and interview quotes from study C, some participants express

an interest and possible meaningfulness in modifying the preoperative time frame if they are able to optimize it. In study B, the preoperative preparation time for the intervention group was on average prolonged by 7 days compared to the aim of the standardized care process. Due to this, one can argue that the intervention and standard care group in study B were not comparable as the duration of their preoperative periods differed. However, our aim was to compare a short-term preoperative exercise intervention to standard care, which in this sense had different preparation times. In addition, it would not have been ethical to prolong the duration of the preoperative period for the control group, as they were not provided with any intervention.

Patients who perceive that they have adequate information, time and support are probably better equipped to take action and also actively participate in decision-making during the preoperative period (205). To change behavior temporarily, for a short time period, such as the preoperative context, might be easier for patients to incorporate than for longer maintenance. A previous study showed that 4 weeks of prehabilitation is sufficient to modify exercise behavior (by increased physical activity levels) (206). Patients might be motivated but not confident in changing their behavior. This has been shown in a new study where confidence scores were lower than the motivational scores (207). This is also consistent with the descriptions in the category “Action depends on reflections of own resources” in our qualitative study (C), which includes the subcategories “confidence in own abilities,” “taking matters into your own hands,” and “motivations to preoperative physical activity and exercise.” In turn, it might contribute to the described gap between awareness and action that emerged as our theme. Thus, even though patients identify multiple motivators for action, the confidence to act needs to be empowered by support from health care professionals. The free text answer “It was interesting to get exercise help from a specialist. It made me feel as I was being taken care of, and thus I have exercised more to show that I can,” from one study participant in study B seen in figure 14 also indicates the need for support to take action.

Within oncological surgery, primarily interventions longer than 4 weeks are evaluated. It is yet to be explored whether and what impact we can observe from preoperative programs as short as 2–3 weeks. When time frames are short, compliance to the intervention is crucial. The compliance in our study was high, probably given that the supervised sessions took place in the participants’ homes. The compliance and intensity could be adequately monitored during the supervised sessions by the physical therapist, and for the self-administered IMT sessions, electronically using the K3 device. One limitation in our study is that we do not know if compliance to the self-reported aerobic and strength exercises are accurate, given that self-reported data often results in under- or overestimations (208). Ideally we should have incorporated activity sensors such as accelerometers, pedometers, or Fitbits. Activity sensors can monitor progress and provide feedback more frequently, thereby also motivating participants. In addition, to reach the aimed intensity of the aerobic and functional strength, we could incorporate even more education regarding the Borg scale as it has previously been addressed that older adults might have difficulties achieving aimed-at intensity levels based on perceived exertion without support (209).

Even though an individual variability in exercise response is expected in a sample of older adults, it is important to address the scientific feasibility as a secondary finding of study B. It was designed as a feasibility study and consequently we did not intend to calculate any treatment effect of the intervention, but to describe the variation of the estimates. In addition, the randomization was imbalanced between the two groups regarding e.g. age. As a reader you need to be aware of this, but in this particular study the imbalance is insignificant in relation to the aim. Only MIP achieved statistical significance within and between groups in favor of the intervention group. This is similar to a previous feasibility study by Valkenet et al. (210). One reason for the lack of effect in the other components of physical performance in our study is probably an insufficient sample size, but perhaps also the short intervention time and the fact that planned intensity was only achieved for the IMT sessions. Improving respiratory muscle strength has previously indicated reductions in postoperative pulmonary complications (PPC's). In healthy subjects, respiratory muscle training has shown to affect physical endurance performance and not just pulmonary function (211). Thus, it is an exercise modality of great importance for overall fitness.

Also worth mentioning are the possible additional effects as a consequence of the exercise intervention, such as the social interaction with the trainer and a sense of context (also mentioned as motivators to physical exercise and prerequisites to enable action in the subcategories of study C), which is harder to quantify. Initiation and awareness of physical exercise prior to surgery might increase tendencies toward increased physical activity and exercise; also postoperatively and after discharge.

Our active intervention was unimodal, only providing physical exercise. Ideally the interventions should have been multimodal, as the care of a patient in the preoperative context is multifactorial. In this study we used nutritional optimization, which was a part of standard preoperative care, and in further studies a more controlled intervention may be added. Nutritional prehabilitation alone or in combination with exercise can decrease LoS (212). Adding a psychological optimization might have provided coping strategies for stress and, therefore, the participants may have been more retentive regarding physical exercise and higher intensities. The effect of psychological interventions in the preoperative context is still scarce (213). A unimodal prehabilitation study from Canada in 2010 (214) did not show any significant effect on functional physical capacity from a bike exercise program in the intervention group, compared to the control group, which was prescribed 30 minutes of walking per day. Later, the same research group showed significant effects in the intervention group when providing a multimodal intervention (215). Possible reasons for the lack of effects in the first study could be the unimodal approach. It could also be a low compliance to the exercise in the intervention group, and also that the outcome measure was the six-minute walk test and thus the control group had specifically conducted what was measured. As previously mentioned, recent RCTs that have proven effects on postoperative complications only included physical exercise as an intervention (69, 70). This indicates that the specific patients included in the trials, in addition to the exercise dose and the outcomes measures chosen, will affect the study results.

Multiple internal and external factors will influence whether and how a preoperative exercise intervention can be tailored and conducted (figure 17). Person-related factors might affect participation and compliance to an intervention, the procedure-related factors will address the magnitude of the surgical effect (incision, surgical localization, general or local anesthesia, duration of surgery, etc.), and factors related to the health care organization will determine if it is even possible and efficient to conduct an extensive preoperative intervention. The effectiveness of the exercise intervention is not just dependent on the dose and content, but also on compliance and adherence to exercise. Thus, preoperative interventions need to be designed to facilitate and stimulate performance. Understanding the patients' perspective during the perioperative pathway is paramount. This multifactorial aspect was also found in study C in relation to patients' attitudes and perceptions.

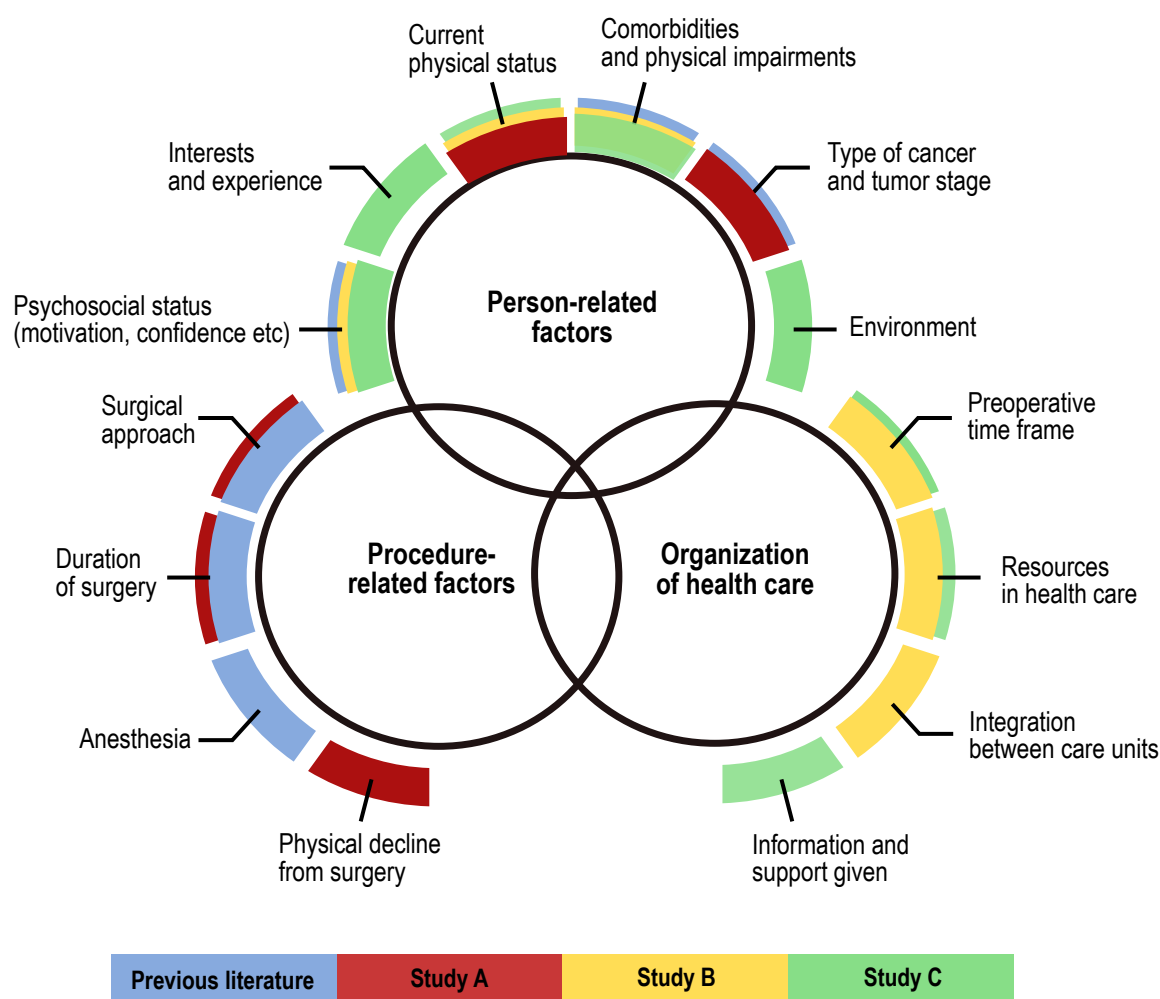


Figure 17. Possible factors to consider when tailoring a preoperative exercise intervention, based on previous literature and the findings from the studies in this thesis.

Our target group was older adults, whereas we incorporated multiple exercise modalities and focused on a functional approach (106), meaning that endurance and strength exercises are embedded in daily activities such as chair stands and stair climbing. We used the Borg CR-10 scale to monitor effort. We are aware that we are not able to standardize the intensity as

thoroughly as you can by using ergometer bikes or gym machines. Nevertheless, our aim was to improve their physical function, not just endurance fitness. In the text material of study C, a big motivator for performing preoperative physical exercise for the older adult was to be able to regain abilities and be independent in everyday life after surgery. Consequently, the home-based approach of the exercise intervention in study B facilitated the goals of the participants as they conduct functional exercise in their habitual environment. Nevertheless, it should also be noted that different individuals may have different preferences regarding the definition of good health and which outcome is of most importance. Preoperative physical exercise might also provide a sense of good health during a time of disease focus. For older adults it has been emphasized that when writing an exercise prescription it is important to educate and motivate the patient with personal goals (76). Targeting individual factors, beyond physical status, which may influence the patients' attitudes towards preoperative exercise can assist in the reasoning between the patient and health care regarding the content of the preoperative period, as one preoperative pathway might not suit everyone.

To sum up, the clinical application of our findings to the dimensions of the MCT is to assess and identify where and how to intervene. This is presumably not only applicable in the field of rehabilitation, but also in the field of prehabilitation (figure 18). The studies included in this thesis can be divided into three components of the MCT: 1) Assessments of current movement capability (papers I and II); 2) Targeted intervention to facilitate preferred movement capability (paper III); 3) The understanding of influential factors in physical, psychological, social, and environmental domains that affect movement (manuscript IV).

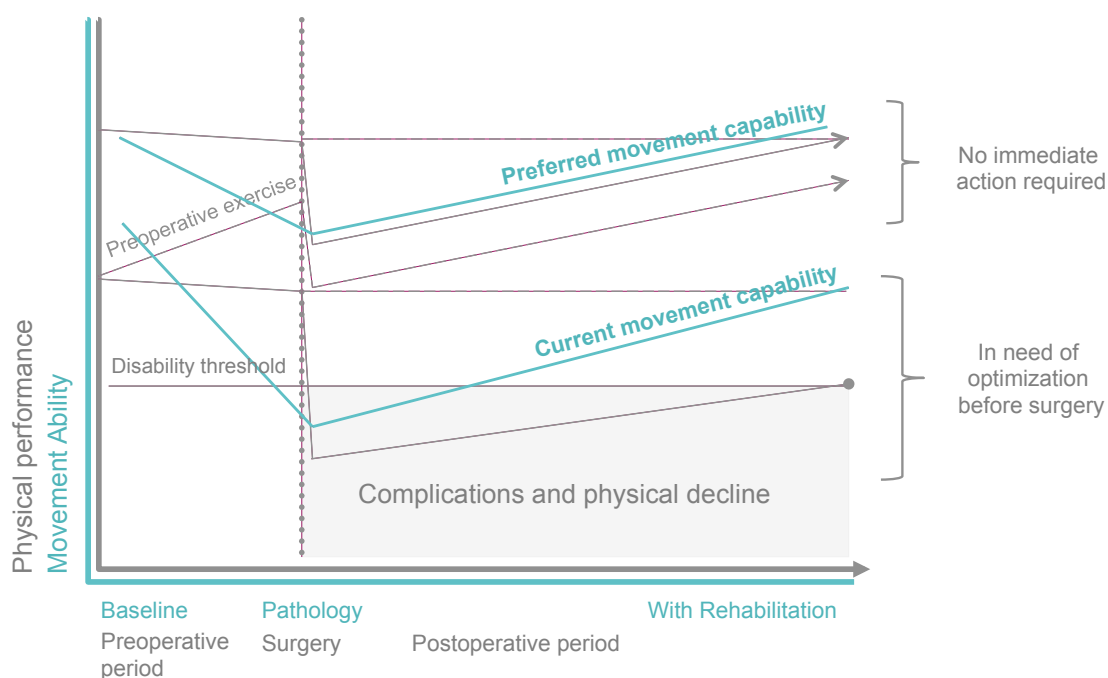


Figure 18. The Movement Continuum Theory (in blue) incorporated into the perioperative context (in grey) modified from Allen et al (37) and reprinted with permission from the publisher Taylor & Francis Ltd (<http://www.informaworld.com>).

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 Internal validity

Some systematic errors need to be addressed in study A as they might lead to an under- or overestimation of the true association. Systematic errors will affect internal validity, which in turn will affect the generalizability of the findings (216). The major methodological limitation, which might result in recruitment bias, was the number of eligible patients declining participation. One may assume that a proportion of non-participants declined due to morbidity and reduced physical function. The inclusion of these patients may have further strengthened the results. The high incidence of complications in the present material leads me to believe that we were able to include a somewhat high-risk sample. The inclusion criteria that incorporate an understanding of the Swedish language can be questioned, and as a consequence, patients not fulfilling those criteria are not reflected in the present analysis. In paper II of study A, there was some inability to follow up given that the outcome was postoperative mobility and only 140 of the 191 participants in the original study sample had data on physical performance and postoperative recovery at discharge. However, the majority of physical performance data lost at follow-up was due to discharge on a weekend, thus this data loss was random (121). Nevertheless, eighteen declined or were not able to conduct the postoperative measurement due to postoperative morbidity, which may have had an impact on the outcome and limited the generalizability of the findings.

There is a risk of informational bias due to the possible misclassification of individuals in the Clavien-Dindo grades (the primary outcome in paper I). This was approached by a double review of the data from the research nurse by the corresponding author and a colorectal surgeon through an audit of the medical records. We also tried to address this by not dichotomizing the outcome in paper I, which is seen in many similar studies. To reduce measurement bias, we provided training sessions for the assessors prior to beginning the study and used an assessment manual to standardize the assessments. Ideally, we would have had one assessor for all of the 197 baseline and 140 follow-up assessments. However, that would have restricted our capacity to include a larger sample and in clinical reality there will always be different physical therapists assessing patients in everyday practice.

Limitations of the different instruments used for assessment are inevitable. The MNA-SF is validated in the older population but not in an onco-geriatric surgical population. The MNA-SF has a total score of only 14 points and a defined risk of malnutrition below 11 points. The study population can basically only reach 12 points due to the malignancy (an acute disease), which leads to an overestimation of malnutrition in the material. The MNA-SF is recommended for a two-step process, whereas patients at risk of malnutrition or having malnutrition should be assessed with the full MNA (217). Low serum albumin can serve as a proxy for a risk of malnutrition, with a low value indicating that the individual has been malnourished for a longer time (catabolic); however, pre-albumin would have given a better short-term estimation. In study A, nutritional status was used as a control variable, and preoperative contact with a dietician in cases of a risk of malnutrition was a part of the

standard clinical pathway in study B. However, for a larger interventional trial I would recommend replacing the MNA-SF with a nutritional assessment validated in the surgical population. Conversely, postoperative delirium (3%) is most likely underreported in our findings. The CAM might not be sensitive enough to detect postoperative confusion, leading to an underestimated incidence. Thus, it should be combined with a test assessing cognitive function such as the MMSE (151). In addition, collection of depression data during the preoperative phase would be desirable given that depression is a considerable risk factor for developing confusion. Ideally, the mental status should have been assessed multiple times during the postoperative period, and not just cross-sectionally on day 4 as in our study, to detect possible changes.

In study A, possible confounders were primarily chosen based on clinical reasoning and scientific literature, and thereafter tested statistically. There is always a risk of residual confounding of unknown risk factors not controlled for. Random errors can occur and are dependent on sample size. To try to prevent this, we kept track of possible overadjustment of the regression models by reviewing the CI when adding and removing variables (218). We reported both unadjusted and adjusted models, exact p-values and confidence intervals to ensure transparency of the precision of the estimates. This will also provide transparency regarding multiple testing conducted in paper I and II. In study B, a randomization should adjust for both known and unknown confounders and divide them equally between the compared groups; due to the small sample size randomization was imbalanced in study B. However, the scope of study B, given the feasibility design, was not to calculate any effect as this was considered to be less impactful for the primary outcomes of that study.

7.2.2 External validity

As external validity is highly affected by the internal validity, the factors discussed above will affect how the findings of these studies and thesis can be generalized outside the reference population. When comparing some demographics (the ones present in our data and in accordance to the ethical applications) between the participants and non-participants in the studies, there were no statistically significant differences regarding age or upper versus lower abdominal cancer, but there were a higher number of females among non-participants in paper I. There were no significant differences regarding baseline physical performance (except for CST), but higher complication rates for non-participants in paper II, and no differences regarding age and sex in paper III. Nevertheless, 42 non-participants declined due to reduced overall health in study A, which might indicate that our study population perceive themselves to be healthier compared to declining participants.

Regarding the age-limit of ≥ 70 years for inclusion in the studies, the choice was based on the fact that an age > 70 years has shown to be a risk factor for several postoperative outcomes such as delirium and pulmonary complications (2, 219), which could increase the chance of including physically vulnerable patients. Nevertheless, the results of paper I in combination with further predictive calculations on the material will aim to provide a screening process including both an easy-to-administer test of physical performance in addition to the standard

risk-factor screening conducted in the clinic. Ideally, this screening process is thought to target high-risk patients regardless of age for future interventional studies. Conclusions drawn from the studies in this thesis will be applicable to subjects similar to the study participants. In the cohort study we did not intend to prove causality.

7.2.3 Trustworthiness (paper IV)

Trustworthiness is investigated to address the quality of content analysis in all phases (preparation, organization, and reporting) of the procedure. It can be assessed by describing the credibility (whether the data and interpretations are reliable), dependability (the stability of data over time and contexts), conformability (objectivity), and transferability (how the findings can be transferred to different settings) of the study (178). A qualitative approach was taken to study C to be able to answer the specific research question. The target population of the qualitative study was older adults scheduled for colorectal surgery. Due to the scope of the study, we found it important not to just include older adults with a positive attitude towards preoperative physical exercise, which could have been the case if the participants of the exercise intervention of study B had been included. To further establish **credibility and dependability** in study C, we used a purposeful sampling method (220), and described the characteristics of included participants on a group level in as much detail as possible (as seen on page 4, and in table 3 of manuscript IV) without jeopardizing the integrity of the individual. For the transparency of each step and decision made, we described the analysis procedure in the method section and the subcategories, building up each category and then the main category in the results section of the manuscript.

Given the complexity of conducting extensive interventions during the short and busy preoperative time frame, flexibility regarding the location of the interviews was needed. The participants chose where they wanted the interview to take place (at home, by telephone, or at the ward on admission). Telephone interviews could result in less information than face-to-face interviews in regard to nonverbal data (221). Nevertheless, in the context of this study, participants may have felt more relaxed and less stressed when being able to conduct the interview without any time restraints or additional transportation to the hospital.

As the research question of study C was formulated based on the challenges in a previous study, the interpretation part of the results may have had a focus on seeking problems to solve. My own professional preconceptions (as a physical therapist) might have led the questions toward trying to understand why patients would not be interested in physical exercise prior to surgery. However, my profession may also have helped me to stay focused on the specific research question addressed in this study. Oili Dahl's professional preconceptions (as a nurse) might have pointed the questions more toward the well-being of the participant and the cancer diagnosis. Therefore, the interview guide was used as a tool to create consistency between the two interviewers and minimize superfluous information. Moreover, the data analysis was conducted by me and two senior researchers from two different disciplines (physical therapy and nursing), thus three independent people with different experience. We held discussions at each step of the analysis and confirmed the

findings of the study together to enhance **conformability**. We also provided 1–2 quotations per category and sub-category in manuscript IV, to enable the reader to connect data and results (178).

A few eligible patients declined participation in the study, mainly due to lack of time prior to surgery. If these had been included, it might have added more descriptions of barriers related to the short time frame of the preoperative period. However, we think that our findings could be **transferable** to older adults scheduled for abdominal cancer surgery with comparable preoperative care processes as in this study (in relation to time and the preoperative clinical pathway). In terms of authenticity, we tried to recruit a sample with different demographics and physical status, which would give a wide range of descriptions of preoperative physical activity and exercise, both positive and negative perceptions.

8 CLINICAL IMPLICATIONS

- Based on our main findings in paper I, assessments of physical performance (as a complement in preoperative risk screening) can help guide health care personnel in preoperative interventions, as well as giving the patients more insight into their preoperative health status and allowing for shared decision-making. Preoperative maximal gait speed could be a feasible and quick tool to further investigate, for assessing physical performance within preoperative clinical care in older adults. It could serve as a tool to include in a CGA, frailty assessment, or risk index. In addition, the results of the physical assessments can be used when prescribing exercise type and dose for an intervention, as well as initiating monitoring of progress.
- Knowing the preoperative physical factors associated with postoperative mobility, which appeared in paper II, can help guide and coordinate discharge or need of further rehabilitation. Moreover, knowing the magnitude of change in physical performance from pre- to postoperative values, also reported in paper II, in this patient group can provide a sense of decline (and variations in decline) attributed to the surgery. The data can also provide more information regarding a possible improvement from a preoperative exercise intervention in relation to the decline due to surgery.
- The findings of recruitment challenges in paper III and the time-related barriers mentioned in study IV can contribute to the knowledge base of preoperative physical exercise with a focus on older adults, and be incorporated into further discussions regarding factors such as preoperative time frames for optimization. A structured approach focusing on the individual needs to be considered when recruiting older patients for preoperative interventions. There is an implication to intervene as soon as possible in the preoperative pathway, maybe even at first suspicion of malignancy regardless of treatment method (chemo/radio/ or surgery), to increase effectiveness and to allow time for the patient to respond and adapt.
- As described in the “support to enable action” category in manuscript IV, patients perceive that guidance and support from health care professionals is paramount during the preoperative period to enable physical activity and exercise. Knowing this can guide healthcare professionals as to the support needed preoperatively, based on stated factors of importance.

9 CONCLUDING REMARKS

This thesis adds a few new pieces to the puzzle to verify and complement the existing research base, with a focus on a population over the age of 70 and various aspects of preoperative physical performance and preoperative supervised physical exercise. The findings emphasize the importance of physical performance-rather than chronological age in the age-group, and the additive value of a functional approach regarding both objectively measured physical performance and physical exercise in preoperative care. In addition, it adds information regarding the magnitude of short-term physical decline and factors associated with postoperative mobility. This is important to understand for postoperative recovery, as well as what may be important to investigate further and include in preoperative interventions involving physical optimization. Patient-reported assessments and outcomes such as patient-reported recovery, patient-specific activities, and satisfaction, as well as the older patients' perspective on preoperative physical exercise can help health care providers to focus on what is important for the patient. Findings from studies B and C together helped us target possible reasons for low recruitment in the intervention study, as well as highlight the importance of preoperative guidance and support.

On the micro level, we need to empower the patient's adaptability and ability, focus on measures that are important for the individual, and involve patients in decision making by providing relevant information regarding their health. On the meso level, we need to improve communication and collaboration between the hospital and primary care regarding prehabilitating and rehabilitating efforts. We also need to unify the expertise from health care and what the patients find valuable, to determine a suitable preoperative pathway.

10 FUTURE DIRECTIONS

Project-specific

- Regarding the data from paper I, sufficient prediction and classification modeling such as random forests modeling, is implied to provide cutoffs for easy-to-use risk stratification models.
- To analyze and interpret the follow-up data on patient-reported outcomes 6 and 12 months after surgery including ADL, patient-reported recovery, physical activity level and HRQoL in both studies A and B.
- Regarding the methodological approach (figure 4) in this thesis, additional gaps need to be filled. First, we need to evaluate the efficacy of the intervention in a larger RCT trial with modifications as described in paper III (continuing in stage 3), and the effectiveness in implementation research. In the larger trial, we need to evaluate exercise dose, especially regarding its effect in only 2–3 weeks of intervention. Second, if useful, the findings should be implemented from research to practice, community, and policy guidelines (stage 4).
- In the long term, if successful, the approach should be evaluated for older adults in other surgical disciplines.

Field-specific

- The evidence on preoperative optimization will probably go from weak to stronger as more large-scale studies are finalized. There is a need for sufficient evidence on the micro and meso levels to reach the macro level (policy) for implementation. Process-evaluation studies are indicated for the implementation of preoperative screening and prehabilitation programs to take research into practice.
- There is a need to improve patient engagement, empowerment, and adaptation. Involving patient-reported outcome measures (PROMs) could provide a patient-focused assessment of the burden and impact of disease by understanding how treatment influences functioning and wellbeing. In addition, the patients' abilities to adapt need to be further investigated.
- There is a need to increase the recruitment of older people into clinical trials for the surgical oncology population, mainly by revising/customizing study design and the recruitment process.
- The “how,” in terms of unimodal versus multimodal prehabilitation as well as intervention dose, need to be developed in different surgical fields and populations.

- Investigate long-term effects from preoperative optimization regarding functional physical capacity and health-related quality of life after discharge, and incorporate health-economic evaluations. There is also a need to connect the whole perioperative continuum and increase collaboration between inpatient and outpatient care on the meso level for the surgical population, as well as to merge the whole trajectory of multimodal and multidisciplinary surgical care.
- Investigate metabolic responses to prehabilitation and how, for example, optimization of preoperative hemoglobin interacts with physical exercise interventions.
- Possible use of technology in terms of devices for monitoring and evaluating, as well as incorporated in interventions such as tele-exercise, should be further investigated in studies.
- There is an indication to further develop the qualitative literature within the research area as it is still sparse. For example, to deepen the knowledge regarding the health care professionals' attitudes toward preoperative physical activity and exercise, as their knowledge and perceptions will affect the communication with the patient in the preoperative context.

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'You can see yourself as a sick old person ... and if that is my self-image I'll adapt to that role and be a sick old person. I can also see myself as a healthy, strong person who likes being physically active and being outside, and if you have that self-image I think you have better chances of getting back to normal life again.'

—Participant of the interview study